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TRANSACTIONS

OF THE

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VOLUME THE FIFTY-FOURTH.

COMPRISING THE REPORT OF THE PROCEEDINGS FOR THE SESSION 1902-1903.

Edited by Samuel G. Shattock.

LONDON:
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1903.

THE Council think it right to state that the authors of the several communications herein published are alone responsible for the statements made or the views put forward by them.

Mar. 29. 1904
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Presidents of the Society.

ELECTED

1846 CHARLES J. B. WILLIAMS, M.D., F.R.S.
1848 CHARLES ASTON KEY.
1850 PETER MERE LATHAM, M.D.
1852 CÆSAR H. HAWKINS, F.R.S.
1853 BENJAMIN GUY BABINGTON, M.D., F.R.S.
1855 JAMES MONCRIEFF ARNOTT, F.R.S.
1857 SIR THOMAS WATSON, BART., M.D., F.R.S.
1859 SIR WILLIAM FERGUSSON, BART., F.R.S.
1861 JAMES COPLAND, M.D., F.R.S.
1863 SIR PRESCOTT G. HEWETT, BART., F.R.S.
1865 THOMAS BEVILL PEACOCK, M.D.
1867 SIR JOHN SIMON, K.C.B., D.C.L., F.R.S.
1869 SIR RICHARD QUAIN, BART., M.D., LL.D., F.R.S.
1871 JOHN HILTON, F.R.S.
1873 SIR WILLIAM JENNER, BART., M.D., G.C.B., D.C.L., F.R.S.
1875 GEORGE D. POLLOCK.
1877 CHARLES MURCHISON, M.D., LL.D., F.R.S.
1879 JONATHAN HUTCHINSON, F.R.S.
1881 SIR SAMUEL WILKS, BART., M.D., F.R.S.
1883 JOHN WHITAKER HULKE, F.R.S.
1885 JOHN SYER BRISTOWE, M.D., F.R.S.
1887 SIR JAMES PAGET, BART., D.C.L., LL.D., F.R.S.
1889 WILLIAM HOWSHIP DICKINSON, M.D.
1891 SIR GEORGE MURRAY HUMPHRY, M.D., LL.D., F.R.S.
1893 FREDERICK WILLIAM PAVY, M.D., LL.D., F.R.S.
1895 HENRY TRENTHAM BUTLIN, D.C.L.
1897 JOSEPH FRANK PAYNE, M.D.
1899 WILLIAM WATSON CHEYNE, C.B., F.R.S.
1902 SIR JOHN BURDON SANDERSON, BART., M.D., D.C.L., F.R.S.

OFFICERS AND COUNCIL

OF THE

Pathological Society of London,

ELECTED AT

THE GENERAL MEETING, MAY 19TH, 1903,

FOR THE SESSION 1903–1904.

President.

SIR JOHN BURDON SANDERSON, BART., M.D., D.C.L., F.R.S.

Vice-Presidents.

R. J. GODLEE. (1)
W. D. HALLIBURTON, F.R.S. (4)
E. KLEIN, F.R.S. (2)
F. W. PAVY, F.R.S. (3)

Treasurer.

P. H. PYE-SMITH, M.D., F.R.S.

Council.

Members of Committee of Section A.

F. E. BATTEN.
R. CRAWFURD.
J. FAWCETT.
H. M. FLETCHER.
S. H. HABERSHON.
H. BATTY SHAW.
C. P. WHITE.

Members of Committee of Section B.

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A. G. R. FOULERTON.
R. T. HEWLETT.
J. McFADYEAN.
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A. E. WRIGHT.

Members of Committee of Section C.

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Members of Committee of Section D.

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Sectional Secretaries.

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G. F. STILL, M.D.

Section B.
W. BULLOCH, M.D.

Section C.
T. G. BRODIE.

Section D.
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General Secretary and Editor of the 'Transactions.'

S. G. SHATTOCK.

Trustees.

SIR SAMUEL WILKS, BART., F.R.S.
J. F. PAYNE.
H. MORRIS.

NOTE.—Section A: Pathological Anatomy and Histology. Section B: Bacteriology. Section C: Experimental Pathology. Section D: Chemical Pathology.
(1) Chairman of Section A. (2) Chairman of Section B.
(3) Chairman of Section C. (4) Chairman of Section D.

Committees.

The members of Council forming each Section (A, Pathological Anatomy and Histology; B, Bacteriology; C, Experimental Pathology; D, Chemical Pathology) constitute committees of reference in the subjects enumerated, with power to add to their numbers in particular cases.

*** *Members are requested to inform the General Secretary of any change of address, etc., which may be necessary.*

LIST OF MEMBERS OF THE SOCIETY.

Honorary Members.

BOUCHARD, C., M.D., Professor of General Pathology, Paris.
CHAUVEAU, A., M.D., Professor of Physiology at the Medical School of Lyons.
KOCH, R., M.D., Director of the Institute for Infective Diseases, Berlin.
The Right Honourable Lord LISTER, F.R.S., F.R.C.S., 12, Park crescent, Portland place, W.
METCHNIKOFF, E., M.D., Chef de Service à l'Institut Pasteur, Paris.
VON RECKLINGHAUSEN, F. D., Director of the Pathological Institute, Strassburg.
RINDFLEISCH, E., M.D., Professor of Pathological Anatomy in the University of Bonn.
ROUX, P. P. E., M.D., Sous-directeur de l'Institut Pasteur, Paris.
SIMON, SIR JOHN, K.C.B., D.C.L., LL.D., F.R.S., 40, Kensington square, W.
WELCH, W. H., M.D., Professor of Pathology, Johns Hopkins University, Baltimore.
WILKS, SIR SAMUEL, Bart., M.D., LL.D., F.R.S., F.R.C.P., 8, Prince Arthur Road, Hampstead, N.W.
ZIEGLER, E., M.D. Professor of Pathological Anatomy, Freiburg.

EXPLANATION OF ABBREVIATIONS.

P.—President.
T.—Treasurer.
V.-P.—Vice-President.
S.—Secretary.
C.—Member of Council.
E.—Editor of the 'Transactions.'

The surnames of Members who have compounded for their subscriptions are printed in this type (**TYPE**). The surnames of Members who have paid the Composition Fee for the 'Transactions' are printed in this type (**Type**).

GENERAL LIST OF MEMBERS.

Elected

1891 ABBOTT, FRANCIS CHARLES, M.S., 34, Weymouth street, Portland place, W.

1879 **ABERCROMBIE**, JOHN, M.D., 23, Upper Wimpole street, W. (C. 1897 1900.)

1896 ABRAHAMS, BERTRAM LOUIS, B.Sc., M.B., 14, Welbeck street, W.

1883 ACLAND, THEODORE DYKE, M.D., 19, Bryanston square, W. (C. 1892-4.)

1891 ADAMI, J. GEORGE, M.A., M.D., Montreal, Canada.

1890 ADAMS, JAMES, M.D., 4, Chiswick place, Eastbourne.

1848 **AIKIN**, CHARLES A., 12, Ladbroke terrace, W. (C. 1864-6.)

1872 AIKIN, CHARLES EDMUND, 12, Ladbroke terrace, W.

1897 ALCOCK, SAMUEL K., M.D., Portland House, Burslem.

1882 **ALLCHIN**, WILLIAM HENRY, M.D., 5, Chandos street, W.

1884 ANDERSON, ALEXANDER RICHARD, 5, East Circus street, Nottingham.

1897 ANDREWES, FREDERICK W., M.D., Highwood, Hampstead lane, Highgate, N. (C. 1900—. Com. Sect. B, 1901—.)

1902 ARMOUR, DONALD, M.B., 89, Harley street, W.

1883 ASHBY, HENRY, M.D., 13, St. John street, Manchester.

1863 BAGSHAWE, FREDERICK, M.A., M.D., 35, Warrior square, St. Leonard's-on-Sea.

1902 BAINBRIDGE, F. A., M.B., 1, Vernon Chambers, Southampton row, W.C.

1856 **Balding**, DANIEL BARLEY, Royston, Herts.

1881 BALLANCE, CHARLES A., M.S., 106, Harley street, W. (C. 1890-2. C. Com. Sect. C, 1901—. S. 1899—1901.)

1875 BARKER, ARTHUR E. J., 87, Harley street, W. (C. 1884-6. V.P. 1896-7.)

1899 BARKER, A. J. G., Kuching, Sarawak, Borneo.

1885 BARLING, GILBERT, M.B., 87, Cornwall street, Newhall street, Birmingham. (C. 1894-7.)

1901 BARNARD, HAROLD L., M.S., 21, Wimpole street, W.

1874 **BARLOW**, Sir THOMAS, Bart., K.C.V.O., M.D., B.S., 10, Wimpole street, W. (C. 1879-81. V.-P. 1894-6.)

1899 BARRATT, JOHN OGLETHORPE WAKELIN, M.D., Bertheaustrasse 6, Göttingen.

1877 BARROW, A. BOYCE, 8, Upper Wimpole street, W.

1881 BARRS, ALFRED GEORGE, M.D., 22, Park place, Leeds.

1853 **BARWELL**, RICHARD, 55, Wimpole street, W. (C. 1862-4. V.-P. 1889-90.)

Elected

1861 **BASTIAN**, H. CHARLTON, M.A., M.D., F.R.S., 8A, Manchester square, W. (C. 1869-71. V.-P. 1885-7.)

1877 BATEMAN, ARTHUR W., B.A., Tenterfield, New South Wales.

1895 BATTEN, FREDERICK E., M.D., 33, Harley street, W. (C. Com. Sect. A, 1903—.)

1876 **BATTESON**, JOHN, 188, Goldhawk road, Shepherd's Bush.

1882 BATTLE, WILLIAM HENRY, 49, Harley street, W. (C. 1898—1901.)

1902 BAUMANN, E. P., M.D., 38, Harley street, W.

1870 BÄUMLER, CHRISTIAN G. H., M.D., University of Erlangen.

1874 BEACH, FLETCHER, M.B., 79, Wimpole street, W., and Winchester House, Kingston Hill, Surrey.

1892 BEADLES, CECIL F., Colney Hatch Lunatic Asylum, N. (C. 1898—1901.)

1879 BEALE, EDWIN CLIFFORD, M.B., 23, Upper Berkeley street, W.

1852 **BEALE**, LIONEL S., M.B., F.R.S., 61, Grosvenor street, W. (C. 1858-9. V.-P. 1874-5.)

1856 BEALEY, ADAM, M.D., M.A., Felsham Lodge, Hollington park, St. Leonard's-on-Sea.

1900 BEATON, ROBERT MILNE, M.B., 7, Dartmouth park road, N.W.

1897 BEDDARD, ARTHUR P., M.D., 44, Seymour street, W.

1865 BEEBY, WALTER, M.D., Rapollo, Liguria, Italy (Nov.—May), and Varallo, Valsesia (May, June, Sept., Oct.).

1880 **BEEVOR**, CHARLES EDWARD, M.D., 135, Harley street, W. (C. 1888-90.)

1883 BENHAM, R. FITZROY, 11, Earl's Court square, S.W.

1886 BENNETT, FREDERICK JOSEPH, 17, George street, Hanover square, W.

1877 BENNETT, Sir WILLIAM HENRY, K.C.V.O., 1, Chesterfield street, W. (C. 1891-3.)

1889 BENTLEY, ARTHUR, J. M., M.D., Mena House, Pyramids, Cairo, Egypt.

1878 BERNARD, FRANCIS R., M.D., Prawls, Stone, near Tenterden, Kent.

1882 BERRIDGE, WILLIAM ALFRED, Redhill, Surrey.

1886 BERRY, JAMES, B.S., 21, Wimpole street, W. (C. 1895-7.)

1903 BEVERIDGE, WILFRID WILLIAM OGILVIE, M.B., R.A.M.C., D.S.O., c/o Sir C. R. McGrigor, Bart, and Co., 25, St. James's square, S.W.

1856 **Bickersteth**, EDWARD R., 2, Rodney street, Liverpool.

1882 BINDLEY, PHILIP HENRY, M.B. Address uncommunicated.

1850 **BIRKETT**, EDMUND LLOYD, M.D., Westbourne Rectory, Emsworth, Hampshire. (C. 1856-7.)

1865 BISSHOPP, JAMES, Mount Pleasant, Tunbridge Wells.

1889 BLACK, ROBERT, M.D., 14, Pavilion Parade, Brighton.

1863 BLANCHET, JEAN B., M.D., M.S., Montreal, Quebec, Canada.

1879 BOILEAU, J. P. H., M.D., Brigade-Surgeon, Army.

1900 BOKENHAM, THOMAS JESSOPP, 10, Devonshire street, Portland place, W.

1900 BOLTON, JOSEPH SHAW, M.D., B.S., B.Sc., The Hall, Claybury, Woodford Bridge, Essex.

1902 BONNEY, W. F. VICTOR, M.D., M.S., 10, Devonshire street, Portland place, W.

1899 BOSANQUET, W. CECIL, M.D., 117*a*, Harley street, W.

1869 BOURNE, WALTER, M.D. (Travelling).

Elected

1861 Bower, Richard Norris (Travelling).

1881 Bowlby, Anthony A., C.M.G., 24, Manchester square, W. (M.G.C. 1884—1900. C. 1886-8, 1895-7. S. 1893-4. V.-P. 1898—1900.)

1895 Box, Charles R., M.D., 2, Devonshire place, Portland Place, W.

1892 Boyce, Rubert William, M.S., F.R.S., Thompson Yates Laboratories, Liverpool University.

1882 Boyd, Stanley, B.S., 134, Harley street, W. (C. 1893-6. V.-P. 1897-9.)

1889 Bradford, John Rose, M.D., F.R.S. 8, Manchester square, W. (C. 1897—1900. C. Com. Sect. C, 1902—. S. 1900-2.)

1880 Bramwell, Byrom, M.D., 23, Drumsheugh Gardens West, Edinburgh.

1889 Bredin, J. Noble, The Vines, Sutton Valence, Maidstone.

1902 Brewerton, Elmore W., 45, Weymouth street, W.

1877 Bridges, Robert, M.B., M.A., Manor House, Yattendon, Berks.

1867 **Bridgewater**, Thomas, LL.D. Glas., M.B. Lond., Harrow-on-the-Hill, Middlesex.

1873 Briggs, Jacob Myers, M.D., Coeymans, New York, U.S.A.

1868 Bright, George Charles, M.D., Cannes, Alpes Maritimes, France.

1902 Brincker, John Augustus Herman, M.B., B.C., Borough Hospital, Waddon, Croydon.

1857 Briscoe, John, 5, Broad street, Oxford.

1885 Briscoe, John F., Westbrooke House, Alton, Hants.

1903 Broadbent, J. F. H., M.D., 35, Seymour street, W.

1860 **Broadbent**, Sir William Henry, Bart., M.D., 84, Brook street, W. (C. 1871-3. V.P. 1882-4.)

1886 Brockatt, Andrew Alexander, M.D., Hazeldean, Malvern.

1884 Brodie, Charles Gordon, Fernhill, Wootton Bridge, Isle of Wight.

1899 Brodie, Thomas Grigor, M.D. (Hon. Secretary, Section C.), 55, Marlborough Mansions, West Hampstead, N.W. (C. 1900—1901. S. Sect. C, 1901—.)

1865 **Brown**, Augustus, M.D., Dovedale, Wimblehurst road, Horsham, Sussex.

1871 Brown, Frederick Gordon, 17, Finsbury circus, E.C.

1903 Browne, H. S. D., 59, Lambeth Palace road, S.E.

1877 Bruce, J. Mitchell, M.D., 23, Harley street, W.

1902 Bruce, Samuel Noble, 15, Queensborough terrace, W.

1890 Brunton, Sir T. Lauder, M.D., D.Sc., LL.D., F.R.S., 10, Stratford place, W.

1898 Bryant, John Henry, M.D., 4, St. Thomas's street, London bridge, S.E.

1855 **Bryant**, Thomas, M.Ch., 27, Grosvenor street, Grosvenor square, W. (C. 1863-6. V.-P. 1877-9.)

1894 Buchanan, George Seaton, M.D., 9, Hammersmith terrace, W.

1890 Buckland, Francis O., M.A., M.B., C.M., Brockenhurst, Hants.

1899 Bulloch, William, M.D., M.B., C.M. (Hon. Secretary, Sect. B), 66, Holland road, Kensington, W. (C. Com. Sect. B, 1901-3. S. Com. Sect. B, 1903—.)

1891 Burghard, Frédéric François, M.D., M.S., 86, Harley street, W.

1880 Burton, Samuel Herbert, M.B., 50, St. Giles' street, Norwich.

Elected

1900 BUSCH, JOSEPH PAUL-ZUM, M.D., Chiswell House, 133, Finsbury Pavement, E.C.

1903 BUSHNELL, FRANK GEORGE, M.D., 20, Athenæum street, Plymouth.

1872 **BUTLIN**, HENRY TRENTHAM, D.C.L., 82, Harley street, W. (M.G.C. 1875-86. C. 1876-8, 1887-9. S. 1884-6. V.-P. 1891-2. P. 1895-7.)

1883 **BUXTON**, DUDLEY W., M.D., 82, Mortimer street, W.

1903 BUZZARD, EDWARD FARQUHAR, M.D., 33, Harley street, W.

1856 **BUZZARD**, THOMAS, M.D., 74, Grosvenor street, W. (C. 1869-70. V.-P. 1881-3.)

1901 CADDY, ADRIAN, M.B., St. George's Hospital, S.W.

1899 CADDY, ARNOLD, 2/2, Harington street, Calcutta.

1893 CALEY, HENRY ALBERT, M.D., 24, Upper Berkeley street, W.

1897 CALVERT, JAMES, M.D., 113, Harley street, W.

1892 CAMPBELL, HENRY JOHNSTONE, M.D., 36, Manningham lane, Bradford.

1891 CARLESS, ALBERT, M.S., 10, Welbeck street, W.

1897 **Carwardine**, THOMAS, M.S., 16, Victoria square, Clifton, Bristol.

1877 CASSON, JOHN HORNSEY, H.B.M. Legation, Teheran, Persia.

1899 CAUTLEY, EDMUND, M.D., 15, Upper Brook street, W.

1864 CAY, CHARLES VIDLER, Deputy Surgeon General. Address uncommunicated.

1863 CAYLEY, WILLIAM, M.D., 27, Wimpole street, W. (M.G.C. 1869-84. C. 1870-1, 1875-8. S. 1872-4. V.-P. 1884-6. T. 1888-93.)

1869 CHAFFERS, EDWARD, Abbotsrood, Milnthorpe road, Eastbourne.

1884 CHAVASSE, THOMAS FREDERICK, M.D., C.M., 22, Temple row, Birmingham.

1901 CHEATLE, G. LENTHAL, 117, Harley Street, W.

1879 CHEYNE, WILLIAM WATSON, C.B., M.B., C.M., F.R.S., 75, Harley street, W. C. 1885-7. (M.G.C. 1890-6. V.-P. 1892-3. P. 1899—1902.)

1902 CHILDS, CHRISTOPHER, M.D., D.P.H., 10, Manchester square, W.

1873 CHISHOLM, EDWIN, M.D., 44, Rosslyn gardens, Darlinghurst, near Sydney, New South Wales [care of Messrs. Dawson, 121, Cannon street, E.C.].

1865 **CHURCH**, Sir WILLIAM SELBY, Bart., K.C.B., P.R.C.P., 130, Harley street, W. (M.G.C. 1869-74. C. 1871-3. V.-P. 1894-6.)

1868 **CHURCHILL**, FREDERICK, M.D., 4, Cranley gardens, Queen's gate, S.W.

1898 CHURTON, THOMAS, M.D., 35, Park square, Leeds.

1861 **CLAPTON**, EDWARD, M.D., Towercroft, 41, Eltham road, Lee, S.E.

1872 CLARK, ANDREW, 71, Harley street, W.

1886 CLARK, FRANCIS WILLIAM, M.B., Victoria, Hong Kong.

1885 CLARKE, JOHN MICHELL, M.D., 28, Pembroke road, Clifton, Bristol.

1881 CLARKE, W. BRUCE, M.B., 51, Harley street, W. (C. 1892-4.)

1899 CLEVELAND, ARTHUR JOHN, M.D., 45, Shooter's Hill road, Blackheath Park, S.E.

1875 **CLUTTON**, HENRY HUGH, M.A., 2, Portland place, W. (C. 1884-6. M.G.C. 1889-94. V.-P. 1892-3.)

Elected

1865 **Coates**, CHARLES, M.D., 10, Circus, Bath.

1892 COLE, ROBERT HENRY, M.D., Moorcroft, Hillingdon, Uxbridge.

1886 COLLIER, WILLIAM, M.D., High street, Oxford.

1888 COLLINS, Sir WILLIAM JOB, M.D., M.S., 1, Albert terrace, Regent's park, N.W.

1878 COLLYNS, R. T. POOLE, Kingsley, Lingfield road, Wimbledon, S.W.

1888 COLMAN, WALTER STACY, M.D., 9, Wimpole street, W.

1882 COLQUHOUN, DANIEL, M.D., Dunedin, New Zealand.

1896 CONNELL, W. T., M.D., Kingston, Canada.

1891 COOK, HERBERT G. GRAHAM, M.D., 22, Newport road, Cardiff.

1858 COOKE, R. T. E. BARRINGTON, 15, St. Nicholas cliff, Scarborough, Yorkshire.

1866 COOMBS, ROWLAND HILL, M.D., Mill street, Bedford.

1892 COOPER, C. DUDLEY,

1903 COOPER, PERCY ROBERT, M.D., B.Sc., Glenthorne, The Downs, Bowdon, Cheshire.

1900 CORNER, EDRED MOSS, M.B., 28, Harley House, Regent's Park, N.W.

1899 CORNER, HARRY, M.D., Brook House, Southgate, N.

1876 COTTLE, WYNDHAM, M.D., 39, Hertford street, W.

1861 **COUPER**, JOHN, 80, Grosvenor street, W. (C. 1870-2.)

1873 **COUPLAND**, SIDNEY, M.D., 16, Queen Anne street, W. (M.G.C. 1882-6. C. 1878-81, 1889-91. S. 1886-8. V.-P. 1892-3. T. 1894—1903.)

1897 CRAWFURD, RAYMOND H. P., M.D., 71, Harley street, W. (C. Com. Sect. A, 1902—.)

1884 CRICHTON, GEORGE, M.D., 96, Earl's Court road, W.

1873 CRIPPS, WILLIAM HARRISON, 2, Stratford place, W. (C. 1883-5. V.-P. 1893-4.)

1877 **CROCKER**, HENRY RADCLIFFE, M.D., 121, Harley street, W. (C. 1887-9. V.-P. 1897-9.)

1886 CROOKSHANK, EDGAR, M.B., Saint Hill, East Grinstead, Sussex. (C. 1890-3. V.-P., 1900-2.)

1875 CROSS, FRANCIS RICHARDSON, 5, The Mall, Clifton, Bristol.

1889 CUFF, ROBERT, M.B., 1, The Crescent, Scarborough.

1871 CUMBERBATCH, A. ELKIN, 80, Portland place, W.

1893 CURTIS, HENRY JONES, M.D., 152, Harley street, W.

1884 DAKIN, W. RADFORD, M.D., B.S., 8A, Grosvenor street, Grosvenor square, W.

1883 DALTON, NORMAN, M.D., 4, Mansfield street, W. (C. Com. Sect. A, 1901-3.)

1873 DAVIDSON, ALEXANDER, M.D., 2, Gambier terrace, Liverpool.

1883 DAVIS, EDWIN HARRY, West Hartlepool.

1859 **Davis**, FRANCIS WILLIAM, R.N.

1879 DAVY, HENRY, M.D., 29, Southernhay, Exeter.

1894 DAWSON, BERTRAND, M.D., 110, Harley street, W.

1899 DEAN, GEORGE, M.D., The Jenner Institute of Preventive Medicine, Queensberry Lodge, Aldenham, Herts.

Elected

1889 DEAN, HENRY PERCY, M.B., M.S., 69, Harley street, W. (C. 1900—1901.)

1899 DE CHAZAL, EDMOND LUCIEN, M.D., Port Louis, Mauritius.

1887 DELÉPINE, SHERIDAN, M.B., C.M., Owens College, Manchester. (C. 1899—1901.)

1880 DENT, CLINTON T., 61, Brook street, W.

1871 DICKINSON, EDWARD HARRIMAN, M.A., M.D. Address uncommunicated.

1858 **DICKINSON**, WILLIAM HOWSHIP, M.D., 9, Chesterfield street, W. (C. 1866-8. S. 1869-71. V.-P. 1872-4. P. 1889-90.)

1890 **DICKINSON**, WILLIAM LEE, M.D., 9, Chesterfield street, W.

1900 DIXON, W. E., M.D., 28, Benson road, Forest Hill, S.E.

1872 DIVER, EBENEZER, M.D., 7, Pittville terrace, Stanshaw road, Portsmouth.

1872 DORAN, ALBAN HENRY GRIFFITHS, 9, Granville place, W. (C. 1882-4. V.-P. 1894-6.)

1893 DOWSON, WALTER, M.D., Newcome, Stanley road, Sutton, Surrey.

1877 DRAKE-BROCKMAN, EDWARD F., 14, Welbeck street, W.

1880 DRESCHFELD, JULIUS, M.D., 3, St. Peter's square, Manchester. (C. 1896-9.)

1896 DREW, DOUGLAS, M.B., 49, Devonshire street, Portland place, W.

1893 DRYSDALE, JOHN HANNAH, M.D., 11, Devonshire place, W.

1865 **DUCKWORTH**, Sir DYCE, M.D., LL.D., 11, Grafton street, Bond street, W. (C. 1877.)

1847 **DUDGEON**, ROBERT E., M.D., 22, Carlton hill, St. John's Wood, N.W.

1902 DUDGEON, L. S., 6, Powis gardens, Bayswater, W.

1871 DUKES, CLEMENT, M.D., B.S., Sunnyside, Rugby.

1877 DUNBAR, J. J. MACWHIRTER, M.D., Hedingham House, Clapham common, S.W.

1877 DUNCAN, ANDREW, M.D., 24, Chester street, Grosvenor place, S.W.

1889 DUNCAN, JOHN, M.D., St. Petersburg.

1884 DUNN, LOUIS ALBERT, M.B., M.S., 51, Devonshire street, Portland place, W.

1879 DURHAM, FREDERIC, M.B., 52, Brook street, W.

1899 EASTES, GEORGE LESLIE, M.B., B.Sc., 35, Gloucester terrace, W.

1901 EASTWOOD, A., M.D., Tuberculosis Commission, Stansted, Essex.

1893 ECCLES, WILLIAM MCADAM, M.S., 124, Harley street, W.

1892 EDDOWES, ALFRED, M.D., 28, Wimpole street, W.

1880 **EDMUNDS**, WALTER, M.C., 2, Devonshire place, Portland place, W. (C. 1892-4. C. Com. Sect. C, 1901-2.)

1882 EDWARDS, F. SWINFORD, 55, Harley street, W.

1889 ELAM, WILLIAM HENRY, New Barnet, Herts.

1883 ELDER, GEORGE, M.D., 17, Regent street, Nottingham.

1867 ELLIS, JAMES, M.D., Coburg street, Fratton, Portsmouth, and California.

1902 EMANUEL, JOSEPH GEORGE, M.B., B.S., B.Sc., 47, Newhall street, Birmingham.

1902 EMERY, WALTER D'ESTE, M.D., 141, Harley street, W.

Elected

1863 Engelmann, George Julius, M.D., A.M., 336, Beacon street, Boston, Mass., U.S.A.

1875 Evans, Julian Augustus, A.M., M.D., 123, Finborough road, Redcliffe square, S.W.

1894 Evans, Willmott H., M.D., B.S., B.Sc., 2, Upper Wimpole street, W.

1879 Eve, Frederic S., 125, Harley street, W. (M.G.C. 1884-94. C. 1885-7. V.-P. 1895-7.)

1876 Ewart, James Cossar, M.B., C.M., F.R.S., School of Medicine, Edinburgh.

1881 Ewart, Sir Joseph, M.D., Bewcastle, Dyke road, Brighton.

1877 **Ewart**, William, M.D., 33, Curzon street, W. (C. 1889-91.)

1859 **Ewens**, John, 17, Redland Grove, Bristol.

1887 Eyles, Charles Henry, Gold Coast Colony.

1897 Eyre, John W. H., M.D., The Bacteriological Laboratory, Guy's Hospital, S.E.

1889 Fairbank, Frederick Royston, M.D., Hillside, Westcott, Dorking.

1894 Fawcett, John, M.D., 26, St. Thomas's street, S.E. (C. Com. Sect. A, 1902—.)

1872 Fenn, Edward L., M.D., Nayland, Colchester.

1902 Fennell, Charles Henry, M.A., M.B., Darenth Asylum, Dartford, Kent.

1872 Fenwick, John C. J., M.D., Long Framlington, Morpeth.

1892 Fenwick, W. Soltau, M.D., 29, Harley street, W.

1885 Féré, Charles, M.D., Médecin de Bicêtre; Boulevard St. Michel 37, Paris.

1897 Fisher, Theodore, M.D., 25, Pembroke road, Clifton, Bristol.

1893 Fletcher, H. Morley, M.A., M.D., B.C., 98, Harley street, W. (C. Com. Sect. A, 1903—. S. Sect. A, 1901-3.)

1872 Forbes, Daniel Mackay, 5, Bedford place, Croydon.

1866 **Foster**, Sir Balthazar Walter, M.D., M.P., 30, Grosvenor road, Westminster.

1891 Foulerton, Alexander Grant Russell, Bacteriological Laboratory, Middlesex Hospital, W. (C. 1900—1901. C. Com. Sect. B, 1903—. S. Sect. B, 1901-3.)

1880 Fowler, James Kingston, M.A., M.D., 35, Clarges street, W. (C. 1887-8.)

1878 Fox, Thomas Colcott, B.A., M.B., 14, Harley street, W. (C. 1892-4.)

1902 Fremlin, H. Stuart, Government Lymph Laboratory, Chelsea Bridge, S.W.

1896 Freyberger, Ludwig, M.D., 41, Regent's park road, N.W. (C. Com. Sect. A, 1902-3.)

1891 Fripp, Alfred Downing, C.B., M.V.O., M.S., 19, Portland place, W.

1864 Frodsham, John Mill, M.D., Streatham, S.W.

1899 Fürth, Karl, M.D., 39, Harley street, W.

1894 Furnivall, Percy, 28, Weymouth street, Portland place, W.

1893 Fyffe, William Kington, M.B., 1, Boullcott street, Wellington, New Zealand.

Elected

1880 GABBETT, HENRY SINGER, M.D., 8, Chiswick place, Eastbourne.

1858 **Gairdner**, Sir WILLIAM TENNANT, K.C.B., M.D., LL.D.Edin., F.R.S., 32, George square, Edinburgh. (V.-P. 1891-2.)

1890 GALLOWAY, JAMES, M.A., M.D., 54, Harley street, W. (C. 1899-1902. Com. Sect. A, 1901-2.)

1870 GALTON, JOHN H., M.D., Sylvan road, Upper Norwood, S.E.

1846 **GARROD**, Sir ALFRED BARING, M.D., F.R.S., 10, Harley street, W. (C. 1851. V.-P. 1863-5.)

1892 GARROD, ARCHIBALD EDWARD, M.D. (HON. SECRETARY, SECT. D), 9, Chandos street, Cavendish square, W. (C. 1898—1901. S. Sect. D, 1901—.

1879 GARSTANG, THOMAS WALTER HARROPP, Englefield, Delamer road, Bowdon.

1872 GARTON, WILLIAM, M.D., Inglewood, Aughton, near Ormskirk, Lancashire.

1902 GASK, G. E., M.B., 45, Weymouth street, W.

1880 GIBBES, HENEAGE, M.B., University of Michigan, Ann Arbor, Michigan, U.S.A.

1853 **GIBBON**, SEPTIMUS, M.D., 39, Oxford terrace, Hyde park, W.

1878 GIBBONS, ROBERT A., M.D., 29, Cadogan place, S.W.

1893 GIBBS, CHARLES, 48, Queen Anne street, W.

1872 GILBART-SMITH, THOMAS, M.D., 68, Harley street, W.

1876 GILL, JOHN, M.D., 30, West mall, Clifton, Bristol.

1881 GLYNN, THOMAS ROBINSON, M.D., 62, Rodney street, Liverpool.

1898 GOADBY, KENNETH WELDON, 21, New Cavendish street, Portland place, W.

1873 GODLEE, RICKMAN JOHN, M.B., M.S., 19, Wimpole street, W. (M.G.C. 1875-84. C. 1877-80, 1891-2. S. 1887-9. V.-P. 1893-4, 1902—. Chairman, Sect. A.)

1878 GOLDING-BIRD, CUTHBERT H., M.B., B.S., 12, Queen Anne street, W. (C. 1885-7. V.-P. 1894-6.)

1902 GOODBODY, FRANCIS WOODCOCK, M.D., 6, Chandos street, W.

1871 GOODHART, JAMES FREDERIC, M.D., 25, Portland place, W. (M.G.C. 1874-86. C. 1876-8, 1886-8. S. 1883-5. V.-P. 1892-3.)

1894 GOSSAGE, ALFRED MILNE, M.B., B.Ch., 54, Upper Berkeley street, W.

1875 GOULD, ALFRED PEARCE, M.S., 10, Queen Anne street, W. (C. 1883-5. V.-P. 1898-1900.)

1870 GOWERS, Sir WILLIAM, M.D., F.R.S., 50, Queen Anne street, W. (C. 1878-9. V.P. 1896-7.)

1888 GRANT, J. DUNDAS, M.A., M.D., C.M., 18, Cavendish square, W.

1900 GREEN, ALAN B., M.A., M.D., B.C., 31, Cheyne court, Chelsea, S.W.

1895 GREEN, CHARLES DAVID, M.D., The Ferns, South street, Romford. (C. 1900-2. Com. Sect. A, 1901-2.)

1867 GREEN, T. HENRY, M.D., 74, Wimpole street, W. (M.G.C. 1869-83. C. 1871-3, 1878-9. S. 1875-6. V.-P. 1886-8.)

1873 GREENFIELD, WILLIAM SMITH, M.D., B.S., 7, Heriot row, Edinburgh. (M.G.C. 1874-81. C. 1877-80. V.-P. 1893-4.)

1886 GREVES, EDWIN HYLA, M.D., Rodney House, Suffolk road, Bournemouth.

Elected

1887 Griffiths, Joseph, M.D., C.M., 63, Trumpington street, Cambridge.
1876 Griffiths, Thomas D., M.D., Hearne Lodge, Swansea.
1900 Grube, Karl, M.D., Neuenahr, Germany.
1899 Gruber, R., M.D., 67, Wimpole street, W.
1902 Grünbaum, O. F. F., M.B., B.C., 30a, Wimpole street, W.

1887 Habershon, Samuel Herbert, M.D., 88, Harley street, W. (C. Com. Sect. A, 1902—.)
1851 **Hacon**, E. Dennis, 269, Mare street, Hackney, N.E. (C. 1872.)
1892 Hadley, Wilfred James, M.D., 58, Harley street, W.
1882 Haig, Alexander, M.D., 7, Brook street, W.
1899 Hall, Arthur J., M.B., 342, Glossop road, Sheffield.
1901 Halliburton, William Dobinson, M.D., F.R.S., Church Cottage, 17, Marylebone road, W. (V.-P., Chairman Sect. D.)
1894 Hallidie, Andrew Hallidie Smith, M.B., 50, Noord street, Johannesburg.
1886 Hamilton, David James, M.B., 41, Queen's road, Aberdeen.
1890 Handfield-Jones, Montagu, M.D., 35, Cavendish square, W.
1886 Handford, Henry, M.D., 6, Regent street, Nottingham.
1902 Handley, William Sampson, M.S., M.D., 41, Devonshire street, W.
1891 Hankin, E. H., Agra, India.
1882 Harbinson, Alexander, M.D., County Lunatic Asylum, Lancaster.
1893 **Harley**, Vaughan, M.D., 25, Harley street, W. (C. Com. Sect. D, 1901—.)
1902 Harman, Nathaniel Bishop, B.A., M.B., Middlesex Hospital, W.; and 34, Queen Anne street, W.
1901 Harmer, W. D., The Warden's House, St. Bartholomew's Hospital, E.C.
1879 Harris, Vincent Dormer, M.D., 22, Queen Anne street, W.
1891 Haslam, William F., 54, Newhall street, Birmingham.
1899 Hawkes, Claude Somerville, Glencairn, Wickham terrace, Brisbane, Queensland, Australia.
1886 Hawkins, Francis Henry, M.D., 73, London street, Reading.
1890 Hawkins, Herbert Pennell, M.D., 56, Portland place, W. (C. 1898—1901.)
1856 **Heath**, Christopher, 36, Cavendish square, W. (C. 1866-7. V.-P. 1879-81.)
1900 Heaton, Charles, Westgate-on-Sea, Thanet, Kent.
1892 Heaton, George, M.B., B.Ch., 47, Newhall street, Birmingham.
1881 Hebb, Richard G., M.A., M.D., 9, Suffolk street, S.W. (M.G.C. 1891—1900. C. 1891-3. 1898—1901. S. 1896-7.)
1884 Hebbert, Charles Alfred, care of C. Baylor, 7, Water street, Boston, U.S.A.
1901 Hédin, Sven Gustav, M.D., Jenner Institute of Preventive Medicine, Chelsea bridge, S.W. (C. Com. Sect. D, 1901—.)
1879 Henderson, George Courtenay, M.D., Kingston, Jamaica, West Indies.
1869 Hensley, Philip J., M.D., 4, Henrietta street, W.
1884 Herringham, Wilmot Parker, M.D., 40, Wimpole street, W. (C. 1894-7.)

Elected

1902 HEWITT, H. E., M.D., Westminster Hospital, S.W.

1892 HEWLETT, RICHARD TANNER, M.D., Bacteriological Laboratory, King's College, Strand, W.C. (C. Com. Sect. B, 1902—.)

1897 HICHENS, PEVERELL S., M.B., B.Ch., 45, Sheep street, Northampton.

1900 HILLIER, WILLIAM THOMAS, Rougemont, Beaconsfield road, St. Albans.

1903 HOBDAY, F., 27, Lower Phillimore place, Kensington, W.

1880 HOBSON, JOHN MORRISON, M.D., Glendalough, Morland road, Croydon.

1854 **HOLMES**, TIMOTHY, 6, Sussex place, Hyde park, W. (C. 1862-3. S. 1864-7. C. 1868. V.-P. 1869-71.)

1878 HOOD, DONALD WILLIAM CHARLES, M.D., 43, Green street, Park lane, W.

1864 HOOD, WHARTON P., M.D., 11, Seymour street, W.

1895 HOPKINS, FREDERICK GOWLAND, M.B., New Museums, Cambridge. (C. 1899—. Com. Sect. D, 1901.)

1900 HORDER, THOMAS J., M.D., B.Sc., 141, Harley street, W.

1897 HORNE, WALTER J., M.B., 27, New Cavendish street, Portland place, W.

1883 HORSLEY, Sir VICTOR, M.B., B.S., F.R.S., 25, Cavendish square, W. (C. 1888-9. V.-P. 1900-1902.)

1896 HORTON-SMITH, PERCIVAL, M.D., B.C., 19, Devonshire street, W.

1880 **HOVELL**, T. MARK, 105, Harley street, W.

1893 HOWARD, ROBERT JARED BLISS, M.D., 31, Queen Anne street, W.

1875 HOWSE, Sir HENRY GREENWAY, M.S., 59, Brook street, W. (M.G.C. 1876-84. C. 1878-81.)

1856 **HUDSON**, JOHN, M.D., 11, Cork street, W.

1874 HUMPHREYS, HENRY, M.D., St. Mary Church road, Torquay.

1897 HUNT, E. L., c/o King, King, and Co., Bombay.

1897 HUNT, GEORGE B., M.D., 47, Albemarle crescent, Scarborough.

1888 HUNTER, WILLIAM, M.D., 103, Harley street, W. (C. 1897-1900.)

1852 **HUTCHINSON**, JONATHAN, F.R.S., 15, Cavendish square, W. (C. 1856-9. V.-P. 1872-3, 1881-3. P. 1879-80.)

1901 HUTCHISON, ROBERT, M.D., 22, Queen Anne street, W.

1884 HUTTON, HENRY RICHMOND, M.B., 8A, St. John street, Manchester.

1880 INGRAM, ERNEST FORTESCUE, Newcastle, Natal, S. Africa.

1886 JACKSON, ARTHUR MOLYNEUX, M.D., Kent County Asylum, Barming Heath, Maidstone.

1865 JACKSON, J. HUGHLINGS, M.D., F.R.S., 3, Manchester square, W. (C. 1872-3. V.-P. 1888-9.)

1875 JALLAND, WILLIAM HAMERTON, St. Leonard's House, Museum street, York.

1897 JAMES, GEORGE T. B., Carlisle mansions, Victoria street, S.W.

1888 JAMES, JAMES THOMAS, M.D., 30, Harley street, W.

1853 **Jardine**, JOHN LEE, Braydell Lodge, Wivelsfield, near Haywards Heath.

1897 **JENNER**, LOUIS, M.B., 4A, Bloomsbury square, W.C.

1881 JENNINGS, WILLIAM OSCAR, M.D., 74, Avenue Marceau, Paris.

1866 JESSOP, THOMAS RICHARD, 31, Park square, Leeds.

1878 JOHNSON, ARTHUR JUKES, Yorkville, Ontario, Canada.

Elected

1876 JOHNSON, CHARLES HENRY, Winton House, Basingstoke, Hants.

1901 JOHNSON, EDWARD ANGAS, M.B., B.S., St. Catharine's Prospect, South Australia.

1888 JOHNSON, RAYMOND, M.B., B.S., 11, Wimpole street, Cavendish square, W. (C. 1896-9.)

1899 JONAS, HERBERT C., M.D., Bear street, Barnstaple.

1853 **JONES**, SYDNEY, M.B., 8A, New Cavendish street, W. (C. 1864-6. V.-P. 1886-7.)

1888 JONES, TALFOURD, M.B., St. Davids, 1, Lascelles terrace, Eastbourne.

1862 **JONES**, THOMAS RIDGE, M.D., 4, Chesham place, S.W. (C. 1882-4.)

1898 KEEP, ARTHUR CORRIE, M.D., M.C., 14, Gloucester place, W.

1867 KELLY, CHARLES, M.D., Ellesmere, Gratwicke road, Worthing, Sussex. (M.G.C. 1872-4. C. 1874.)

1897 KELLY, CHARLES E. M., M.D., Witney, Oxon.

1901 KELYNACK, T. N., M.D., 120, Harley street, W.

1859 KIALLMARK, HENRY WALTER, 5, Pembridge gardens, W. (C. 1875-6.)

1882 KIDD, PERCY, M.D., 60, Brook street, W. (C. 1889-91.)

1871 KING, ROBERT, M.B., Boyfield House, Moulton, Spalding, Lincolnshire.

1852 **KINGDON**, J. ABERNETHY, 6A, Princes street, Bank, E.C.

1901 KLEIN, EDWARD EMANUEL, M.D., F.R.S., Harewood, Riversdale gardens, Twickenham Park, Twickenham. (V.-P., Chairman, Sect. B, 1901—.)

1902 KOENIG, RENÉ PAUL, M.D., 42, Welbeck street, W.

1888 KYNSEY, Sir WILLIAM RAYMOND, K.C.M.G., Oriental Club, Hanover square, W. [Travelling.]

1903 LAKIN, CHARLES ERNEST, M.B., Middlesex Hospital, W.

1878 LANCEREAUX, ETIENNE, M.D., 44, Rue de la Bienfaisance, Paris.

1882 LANE, WILLIAM ARBUTHNOT, M.B., M.S., 21, Cavendish square, W. (C. 1891-3.)

1869 LARCHER, O., M.D.Par., 97, Rue de Passy, Paris. [M. Kliensieck, Libraire, Rue de Lille 11, Paris, per Messrs. Longmans.]

1884 LARDER, HERBERT, Whitechapel Infirmary, Vallance road, N.E.

1897 LATHAM, ARTHUR C., M.D., 44, Brook street, W.

1873 LATHAM, PETER WALLWORK, M.D., 17, Trumpington street, Cambridge.

1876 LAW, WILLIAM THOMAS, M.D., 32, Weymouth street, Portland place, W.

1853 LAWRENCE, HENRY JOHN HUGHES, Picton House, Llandowror, St. Clears. (C. 1873-5.)

1892 LAWRENCE, THOMAS WILLIAM PELHAM, M.B., 12, North hill, Highgate, N. (C. Com. Sect. A, 1901-3.)

1893 LAWSON, ARNOLD, M.D., 12, Harley street, W.

1859 LAWSON, GEORGE, 12, Harley street, W. (C. 1870-1. V.-P. 1884-5.)

1879 LAYCOCK, GEORGE LOCKWOOD, M.B., Melbourne, Victoria, Australia.

1891 LAZARUS-BARLOW, WALTER SYDNEY, M.D., Cecil House, Cavendish road, Sutton, Surrey. (C. Com. Sect. C, 1901—.)

Elected

1901 LEATHES, JOHN BERESFORD, M.B., 10, Park mansions, Battersea park, S.W.
1875 LEDIARD, HENRY AMBROSE, M.D., 35, Lowther street, Carlisle. (C. 1897-1900.)
1877 **LEES**, DAVID B., M.D., 22, Weymouth street, W. (C. 1890-2.)
1867 LEES, JOSEPH, M.D., 21, Brixton road, S.W.
1877 LEESON, JOHN RUDD, M.D., C.M., 6, Clifden road, Twickenham.
1868 LEGG, JOHN WICKHAM, M.D. (Travelling.) (C. 1874-5.)
1902 LEGG, THOMAS PERCY, M.B., 141, Harley street, W.
1892 LEITH, ROBERT FRASER CALDIE, M.B., C.M., B.Sc.
1892 **Leudet**, ROBERT, 72, Rue de Bellechasse, Paris, France.
1897 LISTER, THOMAS DAVID, 50, Brook street, W.
1895 LITTLE, ERNEST GRAHAM GORDON, M.D., 61, Wimpole street, W.
1889 LITTLE, JOHN FLETCHER, M.B., 32, Harley street, W.
1862 **LITTLE**, LOUIS S., 31, Grosvenor street, W.
1896 LITTLEWOOD, HARRY, 25, Park square, Leeds.
1874 LIVEING, EDWARD, M.D., 52, Queen Anne street, W.
1863 **LIVEING**, ROBERT, M.D., 11, Manchester square, W. (C. 1876.)
1881 LUBBOCK, MONTAGU, M.D., 19, Grosvenor street, W.
1897 LUCAS, ALBERT, 9, Easy row, Birmingham.
1873 LUCAS, R. CLEMENT, M.B., B.S., 50, Wimpole street, W. (C. 1883-5.)
1879 LUNN, JOHN REUBEN, St. Marylebone Infirmary; Rackham street, Ladbroke grove road, W. (C. 1897-1900.)
1887 LYON, THOMAS GLOVER, M.D., 1, Victoria square, S.W.

1893 MCFADYEAN, JOHN, M.B., Royal Veterinary College, Great College street, N.W. (C. 1899—. Com. Sect. B, 1901—.)
1896 MACFADYEN, ALLAN, M.D., B.Sc., Jenner Institute of Preventive Medicine, Chelsea gardens, S.W. (C. 1900-3. Com. Sect. B, 1901-3.)
1899 MCGAVIN, LAWRIE H., 6, Mansfield street, Cavendish square, W.
1882 MACKENZIE, FREDERIC MORELL, 29, Hans place, S.W.
1885 MACKENZIE, HECTOR WILLIAM GAVIN, M.A., M.D., 34, Upper Brook street, Grosvenor square, W. (C. 1895-7.)
1870 MACKENZIE, JOHN T., Bombay, India.
1878 MACKENZIE, SIR STEPHEN, M.D., Merrycourt, Great Bookham, Leatherhead, Surrey. (C. 1888-90.)
1902 MACKIE, FREDERIC PERCIVAL, 4, Endsleigh gardens, N.W.
1865 MACLAURIN, HENRY NORMAND, M.D., 187, Macquarie street, Sydney, New South Wales.
1896 MCWEENEY, EDMOND JOSEPH, M.D., M.Ch., 84, St. Stephen's green, Dublin.
1885 MAGUIRE, ROBERT, M.D., 4, Seymour street, W.
1877 MAKINS, GEORGE HENRY, C.B., 47, Charles street, Berkeley square, W. (C. 1889-91. V.-P. 1899-1901.)
1887 MALCOLM, JOHN DAVID, M.B., C.M., 13, Portman street, W.
1892 MANN, HAROLD EDWARD, Alderney.
1890 MANSON, Sir PATRICK, K.C.M.G., M.D., C.M., F.R.S., 21, Queen Anne street, W. (C. 1900-1.)

Elected

1876 MAPLES, REGINALD, Kingsclere, near Newbury.

1868 MARSH, Prof. F. HOWARD, 14, Hertford street, Mayfair, W. (C. 1876-7.) (V.-P 1889-90.)

1887 MARTIN, SIDNEY, M.D., B.S., F.R.S., 10, Mansfield street, W. (C. 1893-6. V.-P. 1900-1902.)

1889 MASON, DAVID JAMES, M.D., Rosemont, Maidenhead.

1867 MASON, PHILIP BROOKES, Burton-on-Trent.

1898 MASTERMAN, ERNEST WILLIAM GURNEY, Surgeon, English Mission Hospital, Jerusalem, Syria.

1892 MASTERS, JOHN ALFRED, M.D., 31, Albert Gate, Hyde Park, S.W.

1884 MAUDSLEY, HENRY CARE, M.D., 11, Spring street, Melbourne, Victoria.

1897 MAXWELL, J. P., c/o E.P. Mission, Amoy, China.

1900 MAXWELL, JAMES LAIDLAW, M.D., E.P. Mission, Yai-nan-fu, Formosa, *viâ* Hong Kong.

1852 MAY, GEORGE, M.B., Reading.

1888 MAY, WILLIAM PAGE, M.D., B.Sc., 9, Manchester square, W., and Helouan, near Cairo, Egypt (November to April).

1881 MAYLARD, ALFRED ERNEST, M.B., 4, Berkeley terrace, Glasgow.

1874 MEREDITH, WILLIAM APPLETON, C.M., 21, Manchester square, W.

1894 MICHELS, ERNST, M.D., 48, Finsbury square, E.C.

1900 MILBURN, LESLIE, Hollywood House, Wimbledon common, S.W.

1882 MONEY, ANGEL, M.D., Hunter street, Sydney, New South Wales.

1901 MOORE, ALFRED, Reculver Villa, Cheam road, Sutton, Surrey.

1899 MOORE, FREDERICK CRAVEN, M.D., The Priory, Ardwick Green, Manchester.

1879 MOORE, NORMAN, M.D., 94, Gloucester place, Portman square, W. (C. 1885-7. M.G.C. 1889-1900. V.-P. 1895-7.)

1875 MORGAN, JOHN H., C.V.O., 68, Grosvenor street, W. (C. 1886-8.)

1874 MORISON, ALEXANDER, M.D., C.M., 14, Upper Berkeley street, W.

1869 MORRIS, HENRY, M.A., M.B. (TRUSTEE), 8, Cavendish square, W. (C. 1877-9, 1884-6. S. 1881-3. V.-P. 1888-9.)

1879 MORRIS, MALCOLM ALEXANDER, 8, Harley street, W.

1894 MORRICE, GEORGE GAVIN, M.D., Holy Trinity Vicarage, Weymouth.

1891 MORTON, CHARLES A., 14, Vyvyan terrace, Clifton, Bristol.

1875 MORTON, JOHN, M.B., Guildford.

1884 MOTT, FREDERICK WALKER, M.D., F.R.S., 25, Nottingham place, W. (C. 1891-3. V.-P. 1899-1901.)

1900 MUIR, ROBERT, M.D., 4, Alfred terrace, Glasgow.

1893 MUMMERY, JOHN HOWARD, 10, Cavendish place, W.

1899 MURRAY, GEORGE R., M.D., 11, Ellison place, Newcastle-on-Tyne.

1885 MURRAY, HUBERT MONTAGUE, M.D., 25, Manchester square, W. (C. 1896-9.)

1894 MURRAY, JOHN, M.B., B.Ch., 110, Harley street, W.

1901 NABARRO, DAVID, M.D., B.Sc., D.P.H., 6, Crown Office Row, Inner Temple, E.C.

1887 NASON, EDWARD NOEL, M.D., 80, Abbey street, Nuneaton.

Elected

1902 NAVRAGORDATO, ANTHONY, St. Thomas's Hospital, Albert Embankment, S.E.

1875 NEWBY, CHARLES HENRY, 63, Victoria road North, Southsea, Hants.

1902 NEWLAND, THOMAS SIMPSON, M.B., Ch.B., North terrace, Adelaide, S. Australia.

1884 NEWLAND-PEDLEY, FREDERICK, 32, Devonshire place, Portland place, W.

1865 NEWMAN, WILLIAM, M.D., Stamford, Lincolnshire.

1895 NIAS, J. BALDWIN, M.D., 5, Rosary gardens, S. Kensington, S.W.

1868 NICHOLLS, JAMES, M.D., Trekenning House, St. Columb, Cornwall.

1876 NICHOLSON, FRANK, M.D., 29, Albion street, Hull.

1864 NORTON, ARTHUR T., C.B., Leyfields Wood, Ashampstead, Berks. (C 1877-9.)

1883 NORVILL, FREDERIC HARVEY, M.B., Dibrooghur, India.

1880 O'CONNOR, BERNARD, M.D., 25, Hamilton road, Ealing.

1873 O'FARRELL, Sir GEORGE PLUNKETT, M.D., 19, Fitzwilliam square, Dublin.

1894 OGLE, CYRIL, M.B., 96, Gloucester place, W. (C. 1899-1901.)

1888 OPENSHAW, THOMAS HORROCKS, C.M.G., M.S., 16, Wimpole street, W.

1892 ORD, WILLIAM WALLIS, M.D., The Hall, Salisbury.

1879 ORMEROD, JOSEPH A., M.D., 25, Upper Wimpole street, W. (C. 1887-9.)

1875 OSBORN, SAMUEL, Maisonnette, Datchet, Bucks.

1881 OWEN, Sir ISAMBARD, M.D., 40, Curzon street, W.

1865 OWLES, JAMES ALLDEN, M.D., Hill View, Woking, Surrey.

1884 PAGET, STEPHEN, 70, Harley street, W. (C. 1894-7.)

1895 PAKES, WALTER CHARLES, Government Laboratory, Pretoria, South Africa. (C. Com. Sect. B, 1901-2.)

1897 PARFITT, CHARLES D., M.D., London, Canada.

1898 PARKER, ARTHUR PERCY, M.B., B.Ch., 27, Beaumont street, Oxford.

1874 PARKER, RUSHTON, M.B., B.S., 59, Rodney street, Liverpool.

1853 PARKINSON, GEORGE, Halsdown House, Exmouth, South Devon.

1901 PARSONS, JOHN HERBERT, M.B., B.S., B.Sc., 28, Great Ormond street, W.C.

1882 PASTEUR, WILLIAM, M.D., 4, Chandos street, W. (C. 1893-6.)

1885 PAUL, FRANK THOMAS, 38, Rodney street, Liverpool.

1865 PAVY, FREDERICK WILLIAM, M.D., LL.D., F.R.S., 35, Grosvenor street, W. (C. 1872-4. V.-P. 1891-2. V.-P., Chairman Sect. C, 1901—. P. 1893-4.)

1868 PAYNE, JOSEPH FRANK, M.D. (TRUSTEE), 78, Wimpole street, W. (M.G.C. 1872-85. C. 1873-5, 1883-5. S. 1880-2. V.-P. 1888-9. V.-P., Chairman Sect. A, 1901-2. P. 1897-8.)

1872 PEARCE, JOSEPH CHANING, M.D., C.M., Montague House, St. Lawrence-on-Sea, Kent.

1879 PEEL, ROBERT, 130, Collins street East, Melbourne, Victoria.

1899 PEMBREY, MARCUS SEYMOUR, M.D., B.Ch., Guy's Hospital, S.E.

Elected

1889 PENBERTHY, JOHN, Royal Veterinary College, Camden Town, N.W.

1887 PENROSE, FRANCIS GEORGE, M.D., 84, Wimpole street, W.

1884 PEPPER, AUGUSTUS JOSEPH, M.B., C.M., 13, Wimpole street, W.

1900 PERKINS, JOSEPH JOHN, M.B., 41, Wimpole street, Cavendish square, W.

1899 PERNET, GEORGE, 77, Upper Gloucester place, N.W.

1888 PERRY, Sir EDWIN COOPER, M.D., Superintendent's House, Guy's Hospital, S.E.

1902 PHEAR, ARTHUR G., M.D., 47, Weymouth street, W.

1878 PHILIPPS, SUTHERLAND REES, M.D., St. Ann's heath, Virginia Water, Chertsey.

1878 PHILLIPS, JOHN WALTER, 30, Stanley street West, Melbourne, Victoria.

1893 PINKERTON, ROBERT A., M.A., M.D., 15, South Norwood hill, S.E.

1884 PITT, GEORGE NEWTON, M.D., 15, Portland place, W. (M.G.C. 1889-97. C. 1890-2, 1896-9. S. 1894-6. V.-P. 1899-1901.)

1876 PITTS, BERNARD, M.A., M.C., 109, Harley street, W. (C. 1888-90.)

1899 PLIMMER, HENRY GEORGE, 16, Cheyne walk, Chelsea, S.W. (C. Com. Sect. B, 1901-3.)

1883 POLAND, JOHN, 2, Mansfield street, Cavendish square, W.

1882 POLLARD, BILTON, M.B., B.S., 24, Harley street, W. (C. 1895-7.)

1850 POLLOCK, JAMES EDWARD, M.D., 37, Collingham place, W. (C. 1862-4. V.-P. 1879-81.)

1870 POORE, GEORGE VIVIAN, M.D., 24A, Portland place, W. (C. 1883-5.)

1879 POTTER, HENRY PERCY, M.D., St. Mary Abbotts Infirmary, Marloes road, Kensington, W.

1866 POWELL, Sir RICHARD DOUGLAS, Bart., K.C.V.O., M.D., 62, Wimpole street, W. (C. 1873-5, 1881-3. S. 1877-9. V.-P. 1887-8.)

1884 POWER, D'ARCY, M.A., M.B., 10A, Chandos street, W. (C. 1891-3. 1899-1902. Com. Sect. A, 1901-2. M.G.C. 1897-1900. S. 1897-9.)

1865 POWER, HENRY, 10A, Chandos street, Cavendish square, W., and Bagdale Hall, Whitby. (C. 1876-7.)

1900 POYNTON, FREDERICK JOHN, M.D., 19, Portman street, W.

1887 PRATT, WILLIAM SUTTON, M.D., Penrhos House, Rugby.

1902 PRICE, F. W., M.B., 1, Maida Vale Mansions, W.

1884 PRICE, JOHN A. P., M.D., 124, Castle street, Reading.

1900 PRICE-JONES, CECIL, M.B., 7, Claremont road, Surbiton, Surrey.

1888 PRIMROSE, ALEXANDER, M.B., C.M., 100, College street, Toronto, Canada.

1882 PRINGLE, JOHN J., M.B., C.M., 23, Lower Seymour street, W.

1895 PURVIS, WILLIAM PRIOR, M.D., 2, Avenue place, Southampton.

1865 PYE-SMITH, PHILIP HENRY, M.D., F.R.S. (TREASURER), 48, Brook street, W. (C. 1874-7. V.-P. 1890-1. T. 1903—.)

1897 RANKIN, GUTHRIE, M.D., 4, Chesham street, S.W.

1890 Ransom, WILLIAM BRAMWELL, M.D., The Pavement, Nottingham.

1891 RATCLIFFE, JOSEPH RILEY, M.B., C.M., Wake green, Moseley.

1887 RAVEN, THOMAS FRANCIS, Broadstairs, Kent.

1870 RAY, EDWARD REYNOLDS, 15A, Upper Brook street, W.

1875 REID, ROBERT WILLIAM, M.D., C.M., 8, Queen's gardens, Aberdeen,

1901 REID, Sr. GEORGE CAULFIELD, Brigstock House, Thornton Heath, Surrey.

Elected

1901 Reissmann, Charles, M.B., St. Peter's, College Town, Adelaide, S. Australia.

1881 Renner, William, Wilberforce street, Free Town, Sierra Leone.

1893 Rennie, George Edward, M.D., College street, Hyde park, Sydney, N.S.W.

1895 Ritchie, James, M.D., 28, Beaumont street, Oxford. (C. Com. Sect. B, 1903—.)

1901 Riviere, Clive, M.D., 19, Devonshire street, W.

1865 **Roberts**, David Lloyd, M.D., 11, St. John's street, Manchester.

1871 Roberts, Frederick Thomas, M.D., 102, Harley street, W. (C. 1883-5.

1878 Roberts, William Howland, M.D., Surgeon, Madras Army.

1888 Robertson, Robert, M.D., The Bungalow, Ventnor, Isle of Wight.

1885 Robinson, Arthur Henry, M.D., St. Mary's Infirmary, Highgate hill, N.

1882 Robinson, Tom, M.D., 9, Princes street, Cavendish square, W.

1888 Rolleston, Humphry Davy, M.A., M.D. 55, Upper Brook street, Grosvenor square, W. (C. 1894-7. 1900-1902. Com. Sect. A, 1901-2. M.G.C. 1895-1900. S. 1898-1900.)

1858 **ROSE**, Henry Cooper, M.D., 16, Warwick road, Maida hill, N.W. (C. 1873-4.)

1875 Rossiter, George Frederick, M.B., Cairo Lodge, Weston-super-Mare.

1877 **ROTH**, Bernard, 38, Harley street, W., and "Wayside," 1, Preston park avenue, Brighton.

1888 Roughton, Edmund Wilkinson, M.D., 38, Queen Anne street, W.

1891 Rouillard, Laurent Antoine John, M.B., Durban, Natal.

1901 Rowland, Sydney, M.A., Jenner Institute of Preventive Medicine, S.W.

1899 Rowlands, Robert P., Guy's Hospital, S.E.

1891 Rüffer, Marc Armand, M.D., The Quarantine Board, Alexandria.

1897 Rundle, Henry, 13, Clarance parade, Southsea.

1900 Russell, A. E., M.D., 107, Lambeth Palace road, Albert Embankment, S.E.

1895 Russell, James Samuel Risien, M.D., 44, Wimpole street, Cavendish square, W.

1891 Russell, William, M.D., 3, Walker street, Edinburgh.

1854 Sanderson, Sir John Burdon, Bart., M.D., D.C.L., F.R.S. (President), 64, Banbury road, Oxford. (P. 1902—. M.G.C. 1869-76. C. 1864-7. V.-P. 1873-4.)

1897 Santi, Philip R. W. de, 15, Stratford place, W.

1902 Sargent, Percy William George, M.B., B.C., St. Thomas's Hospital, S.E.

1886 Saundby, Robert, M.D., 140b, Great Charles street, Birmingham.

1871 Saunders, Charles Edward, M.D., Sussex County Lunatic Asylum, Haywards Heath.

1901 Saunders, E. A., M.B., 49, Harley street, W.

1890 Saunders, Frederick William, M.B., B.C., Chieveley House, Newbury,

1873 Savage, George Henry, M.D., 3, Henrietta street, Cavendish square, W. (C. 1881-3.)

Elected

1882 Savill, Thomas Dixon, M.D., 60, Upper Berkeley street, W.

1902 Schölberg, H. A., M.B., St. Bartholomew's Hospital, E.C.

1891 Schorstein, Gustave Isidore, M.B., B.Ch., 11, Portland place, W.

1901 Scott, Hon. G. H., M.B., B.C., Mertoun House, St. Boswells, N.B.

1902 Scott, S. G., M.A., M.B., Yorkshire College, Department of Medicine, Thoresby place, Leeds.

1899 Seligmann, Charles G., M.B., c/o H. C. Jonas, M.D., Bear street, Barnstaple.

1903 Selous, C. F., M.B., St. Thomas's Hospital, Albert Embankment, S.E.

1877 Semon, Sir Felix, C.V.O., M.D., 39, Wimpole street, W. (C. 1885-7.)

1894 Sequeira, James Harry, M.D., 13, Welbeck street, Cavendish square, W.

1872 Sergeant, Edward, D.P.H., Lancashire County Council, Public Health Department, County Offices, Preston.

1876 Sharkey, Seymour J., M.D., 22, Harley street, W. (M.G.C. 1884-1895. C. 1884-6. V.-P. 1895-7.)

1880 Shattock, Samuel G. (Hon. General Secretary), 4, Crescent road, The Downs, Wimbledon, S.W. (M.G.C. 1884-1900. C. 1885-7, 1893-6. S. 1890-2, 1902—. V.-P. 1896-8. E. 1900—.)

1898 Shaw, Harold Batty, M.D., 7, Devonshire street, W. (C. Com. Sect. A, 1903—.)

1885 Shaw, Lauriston Elgie, M.D., 64, Harley street, W.

1886 **Sherrington**, Charles Scott, M.D., F.R.S., University College, Liverpool. (C. 1894-7.)

1856 **Shillitoe**, Buxton, 2, Frederick's place, E.C.

1875 Siddall, Joseph Bower, M.D., C.M., Conybeare, Northam, Bideford.

1880 Silcock, A. Quarry, M.D., B.S., 52, Harley street, W. (C. 1888-90.)

1901 Singer, Harold Douglas, M.D., St. Thomas's Hospital, S.E.

1892 Slater, Charles, M.B., St. George's Hospital, S.W.

1887 Smallpeice, William Donald, 10, Chester square, S.W.

1879 Smith, E. Noble, 24, Queen Anne street, W.

1887 **Smith**, Frederick John, M.D., 138, Harley street, W.

1894 Smith, Guy Bellingham, M.B., B.S., 24, St. Thomas's street, S.E.

1900 Smith, J. Lorrain, M.D., Queen's College, Belfast.

1873 Smith, Richard T., M.D., 117, Haverstock hill, N.W.

1883 Smith, Robert Percy, M.D., 36, Queen Anne street, W.

1869 Smith, Robert Shingleton, M.D., Deepholm, Clifton Park, Bristol.

1856 Smith, Sir Thomas, Bart., K.C.V.O., 5, Stratford place, W. (C. 1867-9. V.-P. 1877-8.)

1866 Smith, William, Melbourne, Australia.

1870 Smith, William Johnson, Seamen's Hospital, Greenwich, S.E. (C. 1879-81.)

1870 Snow, William Vicary, M.D., Richmond Gardens, Bournemouth.

1888 Solly, Ernest, M.B., Strathlea, Harrogate, Yorks.

1887 Spencer, Walter George, M.S., 35, Brook street, W. (M.G.C. 1894-1900. C. 1896-9.)

1899 Spriggs, Edmund Ivens, M.D., 24, St. Thomas's street, S.E.

1861 Squire, Alexander Balmanno, M.B., 24, Weymouth street, W.

1890 Stabb, Ewen Carthew, 57, Queen Anne street, W.

Elected

1901 STAINER, E., M.B., 60, Wimpole street, W.

1895 STARLING, ERNEST HENRY, M.D., F.R.S., 8, Park square West, Regent's Park, N.W. (C. Com. Sect. C, 1901—.)

1896 STEPHENS, J. W. W., M.D. Address uncommunicated.

1899 STEWARD, FRANCIS J., M.S., 24, St. Thomas's street, S.E.

1900 STEWART, PURVES, M.D., 7, Harley street, W.

1891 STILES, HAROLD JALLAND, M.B., C.M., 5, Castle terrace, Edinburgh.

1897 STILL, GEORGE F., M.D. (HON. SECRETARY, SECT. A), 114, Harley street, W. (C. Com. Sect. A, 1901-3. Sec. Sect. A, 1903—.)

1879 STIRLING, EDWARD CHARLES, C.M.G., M.D., F.R.S., Adelaide, South Australia [care of Messrs. Elder & Co., 7, St. Helen's place, E.C.].

1884 STONHAM, CHARLES, 4, Harley street, W. (C. 1893-6.)

1896 STRANGEWAYS, T. P., St. John's College, Cambridge.

1902 STRICKLAND-GOODALL, J., M.D., 30, Vanbrugh hill, Blackheath, S.E.

1903 STRONG, WALTER M., "Helstonleigh," Champion park, Denmark hill, S.E.

1875 STURGE, W. A., M.D., 29, Boulevard Dubouchage, Nice.

1867 SWAIN, WILLIAM PAUL, 17, The Crescent, Plymouth.

1881 SYMONDS, CHARTERS JAMES, M.S., 58, Portland place, W. (M.G.C. 1884-91. C. 1886-8. V.-P. 1899-1901.)

1886 TARGETT, JAMES HENRY, M.B., M.S., 6, St. Thomas's street, S.E. (M.G.C. 1894-1900. C. 1894-5, 1897-1900. V.-P. 1900-1902. S. 1895-7.)

1870 TAY, WARREN, 4, Finsbury square, E.C. (C. 1881-2.)

1871 TAYLOR, FREDERICK, M.D., 20, Wimpole street, W. (M.G.C. 1879-89. C. 1879-81. V.-P. 1897-9.)

1885 TAYLOR, HENRY H., 10, Brunswick place, Hove, Sussex.

1892 TAYLOR, JAMES, M.D., 49, Welbeck street, W.

1902 THIELE, FRANCIS HUGO, M.D., 7, Hampstead lane, Highgate, N.

1852 THOMPSON, Sir HENRY, Bart., 35, Wimpole street, W. (S. 1859-63. C. 1865-7. V.-P. 1868-70.)

1897 THOMSON, H. CAMPBELL, M.D., 34, Queen Anne street, W.

1891 THOMSON, HENRY ALEXIS, M.D., 32, Rutland square, Edinburgh.

1884 THOMSON, JOHN, M.D., C.M., 14, Coates crescent, Edinburgh.

1901 THOMSON-WALKER, J. W., M.B., 8, Cavendish place, W.

1892 Thorburn, WILLIAM, B.S., 2, St. Peter's square, and Rusholme Lodge, Rusholme, Manchester.

1874 THORNTON, JOHN KNOWSLEY, M.B., Hildersham Hall, Cambridge.

1872 THORNTON, WILLIAM PUGIN, 35, St. George's place, Canterbury.

1900 THURSFIELD, HUGH, M.D., 45, Weymouth street, W.

1880 TIRARD, NESTOR ISIDORE, M.D., 74, Harley street, W.

1884 TIVY, WILLIAM JAMES, 8, Lansdowne place, Clifton, Bristol.

1901 TODD, CHARLES, M.D., Queensberry Lodge, Aldenham, Herts.

1897 TOOGOOD, F. SHERMAN, M.D., The Infirmary, 282, High street, Lewisham, S.E.

1882 TOOTH, HOWARD HENRY, C.M.G., M.D., 34, Harley street, W. (C. 1892-4. M.G.C. 1895-1900.)

Elected

1886 TOTSUKA, KANKAI, Tokio, Japan.

1872 **TOWNSEND**, THOMAS SUTTON, 68, Queen's gate, S.W.

1899 TREDGOLD, ALFRED F., London County Asylum, Woodford Bridge, Essex.

1888 TREVELYAN, EDMOND F., M.D., 40, Park square, Leeds.

1902 TREVOR, ROBERT SALISBURY, M.B., 21, Fitzgeorge avenue, West Kensington, W.

1903 TRITSCH, ISIDOR, Lawn House, Hampstead Heath, N.W.

1851 TROTTER, JOHN W., 4, St. Peter's terrace, York. (C. 1865-9.)

1895 TROUTBECK, HENRY, M.B., B.C., 151, Ashley gardens, S.W.

1859 **TRUMAN**, EDWIN THOMAS, 23, Old Burlington street, W.

1888 TUBBY, ALFRED HERBERT, M.S., 25, Weymouth street, Portland place, W.

1867 TUCKWELL, HENRY MATTHEWS, M.D., 64, High street, Oxford.

1858 TUDOR, JOHN, Dorchester, Dorset.

1863 TURNER, JAMES SMITH, 12, George street, Hanover square, W.

1893 TURNEY, HORACE GEORGE, M.D., M.Ch., 68, Portland place, W.

1858 **TURTLE**, FREDERICK, M.D., Kirkmead, Woodford, Essex.

1880 TYSON, WILLIAM JOSEPH, M.D., 10, Langhorne gardens, Folkestone.

1867 VENNING, EDGCOMBE, 30, Cadogan place, S.W.

1889 VOELCKER, ARTHUR FRANCIS, M.D., B.S., 101, Harley street, W. (C. 1895-7.)

1867 **WAGSTAFFE**, WILLIAM WARWICK, B.A., Purleigh, St. John's hill, Sevenoaks. (C. 1874, 1878-80. M.G.C. 1874-82. S. 1875-7.)

1885 WAKLEY, THOMAS, jun., 16, Hyde park gate, S.W.

1902 WALKER, E. W. AINLEY, M.D., 40, Devonshire street, Portland place, W.

1893 WALKER, NORMAN PURVIS, M.D., 7, Manor place, Edinburgh.

1901 WALLACE, CUTHBERT SIDNEY, 26, Upper Wimpole street, W.

1881 WALLER, BRYAN CHARLES, M.D., Masongill House, Cowan bridge, Kirkby-Lonsdale.

1890 WALLIS, FREDERICK CHARLES, M.B., B.C., 107, Harley street, W. (C. 1898-1901.)

1888 WALSHAM, HUGH, M.A., M.D., B.C., 114, Harley street, W.

1859 WALTERS, JOHN, M.B., Reigate, Surrey.

1892 WARD, ALLAN OGIER, M.D.Edin., 73, Cheapside, E.C.

1903 WARD, EDWARD, M.B., B.C., 21, Park place, Leeds.

1892 WARING, HOLBURT JACOB, M.B., M.S., 37, Wimpole street, W.

1901 WARNER, ALLAN, M.D., 5, Ferndale villas, Harrow.

1891 WATERHOUSE, HERBERT FURNIVALL, M.D., C.M., 81, Wimpole street, W.

1903 WATERS, W. A. P., M.D., 99, Holywell, Oxford.

1890 WEBB, CHARLES FRERE, M.D., New street House, Basingstoke.

1894 **WEBER**, FREDERICK PARKES, M.D., 19, Harley street, W.

1858 **WEBER**, Sir HERMANN, M.D., 10, Grosvenor street, W. (C. 1867-70. V.-P. 1878-80.)

Elected

1864 WELCH, THOMAS DAVIES, M.D. (Travelling).

1894 WELLS, SYDNEY RUSSELL, M.D., 24, Somerset street, Portman square, W.

1892 WESBROOK, FRANK F., M.D., The University of Minnesota, Minneapolis, U.S.A.

1877 WEST, SAMUEL, M.D., 15, Wimpole street, W. (C.1884-6, 1891-3. S. 1889-90. V.-P. 1896-7.)

1888 WETHERED, FRANK J., M.D., 83, Harley street, W.

1891 WHEATON, SAMUEL WALTON, M.D., 10, Restall avenue, Streatham hill, S.W.

1867 WHIPHAM, THOMAS TILLYER, M.D., 11, Grosvenor street, W. (C. 1880-2.)

1869 WHIPPLE, JOHN H. C., M.D., Royal Army Medical Corps.

1877 WHITE, CHARLES HAYDON, 20, Shakespeare street, Nottingham.

1894 WHITE, CHARLES POWELL, M.B., Pathological Laboratory, St. Thomas's Hospital, Albert Embankment, S.E. (C. Com. Sect. A, 1903—.)

1891 WHITE, GILBERT B. MOWER, M.B., B.S., 112, Harley street, W.

1881 WHITE, WILLIAM HALE, M.D., 65, Harley street, W. (C. 1888-90.)

1886 WHITE, WILLIAM HENRY, M.D., 43, Weymouth street, W.

1868 **Whitehead,** WALTER, 17, Market street, Manchester.

1897 WHITFIELD, ARTHUR, M.D., 21, Bentinck street, Manchester square, W.

1869 WILKIN, JOHN F., M.D., M.C., Rose Ash House, South Molton, N. Devon.

1871 WILKINSON, J. SEBASTIAN. Address uncommunicated.

1879 WILLCOCKS, FREDERICK, M.D., 14, Mandeville place, W.

1869 WILLIAMS, ALBERT, M.D. (Travelling).

1858 **Williams,** CHARLES, 48, Prince of Wales road, Norwich.

1866 WILLIAMS, CHARLES THEODORE, M.D., 2, Upper Brook street, W. (C. 1875-8.)

1881 WILLIAMS, DAWSON, M.D., B.S., 2, Agar street, Strand, W.C. (C. 1893-6.)

1881 WILLIAMS, W. ROGER, Beaufort House, Clifton Down, Clifton.

1900 WILLIAMSON, OLIVER K., M.B., B.C., 55, Upper Berkeley street, W.

1863 WILLIS, FRANCIS, M.D., Asheville, N. Carolina, U.S.A.

1889 WILSON, ALBERT, M.D., 1, Belsize park, N.W.

1888 WILSON, CLAUDE, M.D., C.M., Church road, Tunbridge Wells.

1859 WILSON, EDWARD THOMAS, M.B., Montpelier terrace, Cheltenham.

1891 WILSON, THEODORE STACEY, M.D., C.M., 27, Wheeley's road, Edgbaston, Birmingham.

1861 **Windsor,** THOMAS, Medical Library, Boston, Mass., U.S. [care of B. F. Stevens, 4, Trafalgar square, W.].

1889 WINGRAVE, V. HAROLD WYATT, 11, Devonshire street, Portland place, W.

1874 WISEMAN, JOHN GREAVES, Stranraer, St. Peter's Road, St. Margaret's-on-Thames.

1865 WITHERBY, WILLIAM H., M.D., Pitt place, Coombe, Croydon.

1883 WOODCOCK, JOHN ROSTRON, Darlington Court, North road, Bath.

1883 WOODHEAD, GERMAN SIMS, M.D., 6, Scrope terrace, Cambridge. (C. 1891-3. V.-P. 1898—1900. M.G.C. 1899—1900.)

Elected

1879 WOODWARD, G. P. M., M.D., Deputy Surgeon General; Sydney, New South Wales.

1884 WORTS, EDWIN, 6, Trinity street, Colchester.

1903 WRIGHT, ALMROTH EDWARD, M.D., 7, Seymour street, Portman square, W. (C. Com. Sect. B, 1903—.)

1890 WYNNE, EDWARD T., M.B., Gladstone, Queensland.

1884 WYNTER, WALTER ESSEX, M.D., 30, Upper Berkeley street, W.

1872 YOUNG, HENRY, M.B., Monte Video, South America.

1901 YOUNG, HENRY WILLIAM PENNEFATHER, "Eastleigh," London road, Norbury, S.W.

ANNUAL REPORT OF COUNCIL,

1902-3.

PRESENTED AT THE ANNUAL MEETING, MAY 19TH, 1903.

YOUR Council have to report that during the present session twenty-three new members have been elected into the Society, that nineteen members have resigned, and that there have been seven losses by death.

The total number of members at the present time is 710, of whom twelve are honorary.

The death-roll comprises, of Ordinary Members, Lennox Browne, Samuel Fenwick, T. J. Maclagan, F. Manley Sims, and J. W. Washbourn; and of the Honorary Members, Prof. Rudolph Virchow.

The "Laboratory" meetings have been held at University College, the Jenner Institute, and the Medical School of St. Bartholomew's Hospital, and to the Pathological Directors of these institutions the Council offers its best thanks. The fourth meeting, which was to have been held at the Conjoint Laboratories of the Royal Colleges, lapsed by reason of the closure of the laboratories named before the date which had been fixed for that meeting.

At the close of the past year the Council voted a sum of £10 towards the statue which is being erected in Berlin as a memorial to the late Prof. Virchow. This donation was made not only that the Society might officially take part in what had been organised as an international project, but because the Council desired to mark Prof. Virchow's long relationship with

the Society, of which he had been an Honorary Member since the year 1869, and in which he had always taken a great interest.

On previous occasions the Council has (on behalf of the Society) acknowledged Prof. Virchow's position in pathological science by presenting to him a congratulatory address on his eightieth birthday, and a similar address on his seventieth, the Presidents of the Society at these times being Mr. Watson Cheyne and Dr. W. H. Dickinson.

In regardto the 'Transactions' the Council wishes to direct attention to the following facts, which, though not of recent date, are hardly perhaps sufficiently known:

(1) That the work is published in parts during the year, as well as in whole at the end of it, in order to minimise delay in the appearance of communications made by members.

(2) That copies of the volume are annually presented to the libraries of all the universities of Europe and America, as well as to certain other institutions. The countries beyond the United Kingdom to which the 'Transactions' are sent comprise Australia, Canada, India, the United States of America, Japan, France, Germany, Austria-Hungary, Italy, Russia, Spain, Portugal, Belgium, Holland, Denmark, Norway, Sweden, and Switzerland.

The presentation list was, two years ago, enlarged in this extensive manner in order that the communications made in the volume might become as widely known as possible.

In addition to this the Council draws attention to the gratuitous supply of copies furnished to members making communications, and to the care exercised in the reproduction of illustrations.

In these various ways, joined with the changes made in the meetings three years ago, the Council trusts that the efficiency of the Society as an organ for the cultivation of pathology in all its branches has been raised to the highest attainable standard.

Since the last annual report the index of the volumes, from XXXVIII to L inclusive, has been printed and distributed to the members.

The compilation of this, the fourth General Index, was entrusted by the Council to Mr. S. G. Shattock, and in its produc-

tion certain changes have been carried out which, it is hoped, will facilitate the reference to its contents.

Financial Statement by the Treasurer.

During the past year the Society has defrayed the cost of publication of the General Index to Volumes XXXVIII to L, amounting in all to £158 6*s.* 4*d.*, inclusive of a honorarium to the editor.

To meet this and certain additional expenditure upon the 'Transactions' the sum of £250 was realised by the sale of Stock standing in the names of the trustees.

The income during the past year has amounted to £504 2*s.* 4*d.*, of which £429 9*s.* was from subscriptions, £49 19*s.* 5*d.* from the sale of 'Transactions,' and £23 13*s.* 11*d.* dividend on Consols.

On the expenditure side the total amount paid for printing and illustrations (including about £30 for reprints distributed gratuitously to writers of papers) was £396 4*s.*

The total expenditure has amounted to £831 13*s.* 9*d.*, and the total receipts to £762 11*s.*, which include the payment for the General Index and the sum acquired by the sale of Stock. There is therefore a deficit which amounts to £69 2*s.* 9*d.*

The amount of Stock now held by the Society in Consols is £854 6*s.* 3*d.*

THE PATHOLOGICAL SOCIETY OF LONDON.

Statement of Receipts and Payments from 15th May, 1902, to 15th May, 1903.

RECEIPTS.

	£ s. d.	£ s. d.	£ s. d.
Petty Cash in hand, 15th May, 1902 ..			3 1 2
378 Subscriptions at £1 1*s.*	396 18 0		
Less 3 Subscriptions paid in error..	3 3 0		
		393 15 0	
24 Entrance Fees at £1 1*s.*		25 4 0	
1 Life Composition Fee		15 15 0	
			434 14 0
Sale of Transactions			49 19 5
9 Fees for Agenda Notices at 2*s.* 6*d.*			1 2 6
Dividends on Consols			23 13 11
Proceeds of Sale of Consols (£259 16*s.* 11*d.*)			250 0 0
			762 11 0
Balance due to Bank			69 3 0
			£831 14 0

PAYMENTS.

	£ s. d.	£ s. d.
Balance due to Bank—15th May, 1902.....		76 1 10
Meetings:		
Rent of Rooms	73 10 0	
Refreshments and Attendance at Meetings ..	21 0 0	
Microscopes	25 19 6	
		120 9 6
Transactions:		
Printing, Binding, etc., for Vol. LIII	266 15 2	
Illustrations " "	116 7 4	
Illustrations for Vol. LIV	13 4 2	
General Index for Vols. XXXVIII–L	108 6 4	
Editor " "	50 0 0	
		554 13 0
Secretariat and Treasury:		
General Printing and Stationery	22 13 3	
Council Notices	2 0 0	
Secretarial Assistance	15 15 0	
Collection of Subscriptions	15 15 0	
Mr. Clarke's Fee	5 5 0	
		61 8 3
Subscription to the Virchow Memorial Fund		10 10 0
Cost of Power of Attorney for Sale of Consols		0 11 6
Bank Charges		0 13 9
Petty Cash Expenditure		7 5 11
		831 13 9
Petty Cash in hand		0 0 3
		£831 14 0

Audited and approved, 18th May, 1903.

SIDNEY COUPLAND, M.D., *Treasurer.*
S. G. SHATTOCK, *Hon. Secretary.*

S. N. BRUCE,
LOUIS JENNER, M.B., } *Auditors.*

NOTE.—The sum of £854 6*s.* 3*d.* is invested in Consols.

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THE

PRESIDENTIAL ADDRESS

BY

SIR JOHN BURDON-SANDERSON, BART., M.D., F.R.C.P., F.R.S.,

REGIUS PROFESSOR OF MEDICINE, UNIVERSITY OF OXFORD.

THE PATHOLOGY OF INFECTION.

THE proposal of the Council of the Pathological Society that I should take the office of President was one that I accepted with great pleasure, as an indication of the good-will of those whose good-will I most esteem. The honour you have done me in my old age in bringing me back as your President after so many years' absence from your meetings, I take as an expression of your approval of the efforts which I have made, however ineffectually, to vindicate the claim of the science which this Society represents—the science of pathology—to a place of equal honour with the other sciences, and at the same time to maintain its close relationship with the practice of medicine and surgery.

In common with the older sciences, pathology seeks to investigate the "causes of things"—the relation to each other of the phenomena which in endless sequence constitute the life of the organism, no less in disease than in health. Fifty years ago the only part of pathology which had reality in it was pathological anatomy. On this foundation, and more particularly on the new anatomical facts which towards the middle of the last century the microscope had revealed, Virchow had

founded the new science. In his hands and in those of the men who worked with him, first at Würzburg and afterwards at Berlin, the science rapidly grew into what it has been for the past forty years, comprising in its widened scope not merely the structural changes which result from disease, but the processes which produce them.

Considering that this is our first meeting since the death of the great master, it might seem appropriate that I should take as my subject the inestimable services which he has in his long life rendered to medicine; that I should remind you of the "cellular pathology" and of the succession of discoveries relating to the minute anatomy of inflammation and tubercle, to the genesis of morbid growths, to the processes of degeneration —in short, to all the fundamental processes of disease which were at that time within reach of anatomical investigation. For several reasons I feel reluctant to attempt the task this evening. The time at our disposal would be inadequate, and nothing that I could say would be new to you. Those who are old enough to remember the dim twilight of fifty years ago can perhaps better realise the claims of Virchow to our grateful remembrance than their successors; but all of us who are earnestly working for the advancement of medicine, whether at the bedside or in the laboratory, feel that they belong to his school and are directly or indirectly his disciples. The observations for which I ask your kind indulgence will relate to a subject which some thirty years ago occupied much of my attention. It had no prominent place in the "cellular pathology" which Virchow, Recklinghausen, and Cohnheim had taught us, but nevertheless has now so close a relation to it that I felt justified in designating it on a former occasion the "cellular pathology of to-day."[1] For, the encounter of disease-producing agents with the living organism presents to us problems which are as truly problems of cellular pathology as are those relating to the processes of inflammation, tubercle, or cancer. The subject on which I am about to speak is the pathology of infection. Before I proceed further I wish to observe that had I known that my friend Dr. W. H. Welch would make infection the subject of the Huxley Lecture, I

[1] "Address to the Thirteenth International Congress," 'The Lancet,' August 25th, 1900, p. 563.

would have selected some other topic for this evening. As, however, the aim I have in view is humbler and very different from his, I do not apprehend that I shall say anything discordant with that admirable exposition of the experimental data relating to immunity. The purpose I have placed before myself is to translate into language which would have been intelligible to the pathological student of twenty years ago the technical language which is unavoidable in dealing with notions which have, so to speak, sprung fresh from the laboratory, and have not yet had time to clothe themselves in plain English.

May I for a moment ask your attention to the form in which the question of the nature of infection presented itself at the end of the sixties? Lister had taught us the etiology of traumatic inflammation and of the diseases which are associated with it. From Chauveau[1] we had learned that in the liquid contagia of many diseases communicable by inoculation—glanders, clavelée, vaccinia—the morbific agent could be separated from the liquid in which it was suspended by mechanical means such as filtration or subsidence; and it had been inferred from this that all such morbific agents were particulate. Villemin[2] had shown that tuberculosis could be communicated with certainty by inoculation. I myself[3] did my best to complete the work which Villemin had begun, by exploring the channels by which the tuberculous process is disseminated within the organism and demonstrating its intimate relation with the lymphatic system. Then followed the excellent experimental and histological work done by Klein,[4] which did the utmost that could be accomplished by the technical resources which were then at the disposal of the pathologist. But notwithstanding these discoveries, the central question remained unanswered. It was not known whether the tuberculous process depended for its origin on a specific infection or owed its characteristic peculiarities to pre-existing structural conditions, for experiment seemed to show that subacute inflammatory processes of non-infective

[1] "Détermination expérimentale des Éléments qui constituent le Principe virulent dans le Pus varioleux et le Pus morveux," 'Comptes Rendus,' February, 1868.

[2] 'Étude sur la Tuberculose,' Paris, 1868.

[3] "On the Communicability of Tubercle by Inoculation," 'Tenth and Eleventh Reports of the Medical Officer of the Privy Council,' London, 1868 and 1869.

[4] 'Anatomy of the Lymphatic System,' London, 1873–75.

origin affected the lymphatic system and followed the course of the lymphatic channels in the same way as tuberculous ones, so that the latter could not be considered as more effective than the former. It was not until several years later that unequivocal evidence of the specificity of tubercle was obtained, not by the discovery of the *corpus delicti* itself, for that did not happen until still later, but by the experiments of Salomonsen,[1] in which it was shown that if a minimal quantity of tuberculous material is introduced into the anterior chamber of the eye of a rabbit no inflammatory reaction follows, but after an incubation period of two or three weeks tuberculous nodules appear on the iris, the process eventuating in general tuberculosis. It is not a little remarkable that, at the very time that Salomonsen was engaged with Cohnheim in these experiments, Koch was perfecting that great discovery which was the foundation of the bacteriological method—the discovery that the bacillus of anthrax could be cultivated in successive generations *outside of the body*, and that these generations retained the power of communicating the disease for an unlimited period. It thus came to pass that the years from 1877 to 1879 were among the most notable in the history of our science; for while Salomonsen's discovery afforded to the many searchers after the specific micro-organism of tubercle—among whom one of the foremost in this country was my predecessor in this chair, Mr. W. Watson Cheyne—the assurance that their search would eventually be successful, Koch's discovery furnished the method by which that success was rendered possible.

Let us hasten over the next eight years, during which new specific forms of micro-organisms were observed and discriminated from each other in rapid succession, and pass on to the next important step in the investigation of the process of infection—the discovery by Flügge and Nuttall[2] at Breslau, and by Buchner[3] at Munich, of the fact that in certain animals the liquor sanguinis is possessed of alexeteric properties by

[1] "Sur l'Inoculation de la Tuberculose, spécialement à l'Iris du Lapin," 'Nordiskt Medicinskt Arkiv.,' 1879, vol. xi.

[2] "Studien über die Abschwächung virulenter Bacterien," etc., including Nuttall, "Experimente über die bacterienfeindlichen Einflüsse des thierischen Körpers," 'Zeitschrift für Hygiene,' 1888, vol. iv.

[3] "Untersuchungen über die bacterienfeindlichen Wirkungen des Blutes und Blutserums," 'Archiv für Hygiene,' 1890, vol. x, p. 84.

virtue of which it may contribute to the defence of the organism; and that, in animals in which the power of resisting specific infections has been acquired by immunisation, this power can be transmitted to other individuals by the serum. It does not lie within my scope to speak of the value of this discovery as the harbinger of a new therapeutic method. I wish only to dwell on its influence on the progress of research. To the scientific investigator of the infective process it at once opened new possibilities, the result of which has been that during the last ten years the inquiry into the nature of the alexeteric properties of the blood, whether natural or acquired, has been carried out with extraordinary zeal and success in Germany, France, Scandinavia, Russia, Italy, Japan—as well as in the laboratories of this country and of America. But the results which have been gained present to the student who desires to bring them into intelligible relation with each other, difficulties which, if I am not mistaken, are greater than any which he has to encounter in other branches of pathology. In attempting to discuss them, however imperfectly, I am not vain enough to imagine that I shall be able to add to the knowledge of those members of the Society who are conversant with the subject. The utmost that I can hope for is to be of some use to those who are perplexed by the multiplicity of the experimental data which have been presented to them, and (to use a homely expression) who find it difficult to see the wood because of the trees. The main source of this difficulty is no doubt the rapidity of progress—the number of new experimental results which present themselves to us year by year and month by month. A few years ago the contest seemed to be between infected organism and infecting microbe. Now we have also to do with toxines and antitoxines. In the language of a century ago, a transition has taken place from solidism to humoralism; and even the old words have been revived. Happily the change does not depend, as was wont to be the case at former periods in the history of medicine, on a swing of the pendulum of medical opinion, but on the real progress of experimental investigation. Every advance brings us nearer to the scene of action, and thus enables us to see things on a larger scale and in more detail. In our attack on the citadel of knowledge, the obstacles are the more formidable the nearer we approach the breach. Far from finding the work cut

out for us easier, it is ten times more difficult. To the microscopical methods we used before we have now to add chemical ones. If we had to do with substances of known constitution which could be recognised by their chemical reactions, it might be otherwise; but as yet we are far removed from this knowledge. We gratefully learn from the physicist and chemist how to use exact methods and instruments. Even as regards these we find that we must largely depend on ourselves. For the methods which in the present investigation have done most for us—such, *e. g.*, as the use of the centrifuge, filtration through porcelain, and, to mention the most recent, the cytoclastic method contrived by Mr. Sydney Rowland—have been all devised by pathologists themselves. In the interpretation of the newly discovered properties of the circulating blood and of the tissue juices on which immunising processes depend, I hope to be able to show you as I proceed that we have already received invaluable direct assistance from the exact sciences; but the history of pathology leads us to believe that the most important work will still be done by men who, like Virchow, Cohnheim, Lister, Koch, and Ehrlich, are themselves pathologists.

The consideration of a complicated question like that of infection can often be best entered upon from the point of view of the prevalent notions which relate to it, for in general such notions contain a kernel of truth. Now there are two points relating to infection about which all are agreed. One of these is that when a contagium enters the human or animal body its encounter with the living organism is of the nature of a struggle between two opposing tendencies. We may accept this notion of reciprocal counteraction or antagonism as fundamental, and allow it free scope in our speculations as to the nature of infection, not merely because it is in harmony with observed facts with which we have been long familiar, but also because it is a necessary corollary to the one biological law to which there is no exception,—the law that in the living organism every part, every organ works together with the rest for the maintenance and efficiency of the whole, and consequently for the counteraction of whatever is hostile to that end. The existence in the environment of specific disease-producing poisons is a fact, like that of the origin of evil in the moral world, behind which we need not at present strive to penetrate.

The liability to infection which this fact implies must, in accordance with the law of adaptation, be associated with the power of counteracting it. Our question, therefore, is not why we are provided with the means of guarding against these risks, but how contagia act and how the organism reacts against their attacks. The progress of research affords ground for believing that the principle of antagonism has an almost unlimited scope in its application to the process of infection. The old notion that every bane has its antidote is so far true that every *injurious* substance which is capable of being assimilated (in the physiological sense) by a living cell is also capable of exciting in it an abnormal reaction antagonistic to the first. We have long recognised this power of reaction in the cells of the animal body, but Dr. Walker,[1] by his previous studies on the bacillus of typhoid fever, and still more by the experiments published only the other day, has given reason for believing that it is also possessed by the bacillus itself. He has shown that when the bacillus of typhoid fever is grown in a bacteriolytic medium, those bacilli which escape dissolution acquire a higher degree of virulence. In other words, the anti-bacterial reaction of the medium excites in the bacilli which evoked it an anti-antibacterial—*i. e.* a pro-bacterial—reaction which is, of course, equivalent to an increase of virulence.

A second point about which there is also complete agreement is that of *specificity*. I have already referred to the four or five years during which the discovery of the specific cause of tubercle was anticipated and the micro-organism itself sought for, just as the discovery of the planet Neptune was anticipated by the astronomers Adams and Leverrier. Since then we have been furnished with equally unequivocal evidence of the specificity of many other diseases which were before of doubtful etiology. But the most striking result of all has been the discovery of the close analogy between the specificity of man and of the higher animals and that of their diseases. This analogy may be expressed by saying that species in animals and species in infective diseases have this in common, that they can both be distinguished by characteristic peculiarities in the liquid part of the circulating blood—characteristics which might be called

[1] 'Journal of Pathology,' March, 1902, and 'British Medical Journal,' October 18th, 1902.

chemical were it not that, although they belong not to cells but to their fluid environment, they are physiological or pathological, and not such as the chemist could take cognizance of. On this interesting subject time will not allow me to enter.

If I have not occupied too much of your time with these general considerations, I will ask your permission to pass on to the discussion of the two forms in which the infective process presents itself—infection by toxine and infection by bacteria. In doing so I will ask you to regard these processes exclusively from the pathological point of view. I am anxious that we should as far as possible confine our attention to what happens in the tissues and structures of the infected organism when attacked by the infecting toxine or bacterium as the case may be. Of the first kind of infection diphtheria is the typical instance. Its toxic action can be measured with assured accuracy by determining how much is just enough to kill a given test animal in a given time. A certain quantity of horse serum prepared by the now familiar method of immunisation is proved by experiment to counteract that action—*i. e.* in technical language, to neutralise the *minimal lethal dose*. This experiment, which has been repeated thousands of times, suggests the existence in toxine and serum of two bodies which enter into chemical combination, but when we seek for the evidence that this is so we encounter great difficulties. If the combination of the two antagonistic substances is a chemical one, it must be indicated by chemical reactions capable of being expressed in chemical language. In judging of chemical neutralisation we have recourse to a chemical test or indicator. In the present instance our indicator is not chemical but pathological. The reagent used is not a chemical reagent in a test bottle, but a living guinea-pig in a cage. We are able to observe the pathological effects, but of the substances which produce them we have as yet no exact knowledge. We shall see as we proceed that certain concomitant phenomena of infection are already accessible to chemico-physical investigation, but this cannot yet be said to be the case as regards the essential process of infection and counter-infection. We can best judge of this by considering what we know as to the essential nature of the action of the toxine of diphtheria.

The quality which stands first is lethality. This we measure

in terms of the M.L.D. (minimum lethal dose) unit. But lethality is not all. All toxines in moderate dose do something else. Side by side with the lethal process there is another process, the effects of which tend in the opposite direction. Its nature may be compared to what in physiology is called stimulation. For, just as the introduction of a sapid substance into the mouth evokes a corresponding specific sensation, so when a toxine enters the organism it calls forth an equally specific reaction or response. It is scarcely needful to point out that this response must have its seat in the living organism or in the cells of which it is constituted, and that, like other responses to stimulation, there is no constant relation between the intensity of the response and that of its exciting cause. It is still more important to notice that, although its effects extend not only to the living cells, but to the medium in which they live, the action itself is physiological or vital.

The two properties I have endeavoured to characterise, the lethal effect and that of inducing an antidotal or protective action, are so different that it may seem superfluous to contrast them; but their association in the process of infection suggests the question of the nature of the connection between them. There are many indications that these two actions are not necessarily dependent on each other. Let us refer to one or two experimental facts. If, after a lethal dose of toxine has been administered to a guinea-pig, a dose of antitoxine slightly larger than that necessary to antagonise the toxine *in vitro* is given immediately, the lethal effect is averted. But if the antidote is delayed, as in the experiments of Dönitz,[1] the quantity of antitoxine required to prevent death must be correspondingly increased until eventually no amount of it is adequate. The lethal process, therefore, is one of which you can measure the duration in minutes, whereas the reaction is a process of protracted development. The separateness, or rather separableness, of the one process from the other is still more strikingly proved by a remarkable series of experiments, also relating to tetanus toxine, made a year ago by Dr. Ritchie.[2] He found that by sub-

[1] "Ueber das Antitoxin des Tetanus," 'Deutsche medicinische Wochenschrift,' 1897, vol. xxiii, p. 428.

[2] "Artificial Modifications of Toxins, with special reference to Immunity," 'Journal of Hygiene,' 1901, vol. i, p. 125.

jecting tetanus toxine to the action of very dilute hydrochloric acid for a limited period, it is possible so to modify active tetanus toxine as to deprive it of its lethality while retaining its power of exciting antagonistic action. He was thus able to use it at once in much larger dose than would otherwise have been possible, and consequently to bring up his animals very rapidly to such a degree of immunity that (in one series of experiments) after a very few days they tolerated more than a hundred times the minimal lethal dose.

I have mentioned the experiments of my colleague first as being best known to me, but there are others which exemplify the same principle—that of the separableness of the two actions of a toxine. The reason why it was necessary in Ritchie's experiment to subject tetanus toxine to a mitigating process before using it to immunise a guinea-pig was that the susceptibility of that animal to the virulent action of the tetanus toxine is so great that the reactional process is anticipated by the lethal. In the rabbit the susceptibility is so slight that there is no difficulty in obtaining immunity in the usual way, even when unmitigated toxine is used. It may, indeed, be stated generally that animals which are wholly insusceptible to the poisonous action of a toxine may notwithstanding be immunised by it and yield antitoxic serum.

Just as diphtheria and tetanus have served us for the exemplification of the process of infection by soluble toxines, so we may take cholera as an instance of infection by microbes. We choose cholera for the reason that the fundamental experiment of Pfeiffer,[1] which has led to so many important discoveries, related to the cholera vibrio. I must occupy a few moments in recalling the conditions of that experiment to your attention. In the earliest experiments on infective products (I refer to Klein's and my own experiments in the seventies) the peritoneal cavity of the guinea-pig was used as constituting an admirable cultivation chamber containing endothelial elements prone to proliferate and leucocytes prepared to incorporate whatever particles were presented to them. The value of the method is now much greater than it was then. The experiment I have just mentioned consists in this—that you introduce into the peritoneum

[1] Pfeiffer, "Ein neues Grundgesetz der Immunität," 'Deutsche med. Wochenschrift,' 1896, Nos. 7 and 8.

cholera vibrios of mitigated virulence in less than lethal dose. These are followed in a day or two by others of virulent cultures, and those by successors in increasing doses. The effect of the proceeding is that the guinea-pig becomes "immune," the signs of which change are (1) that fresh vibrios in many times the lethal dose can be introduced without lethal result; (2) that the vibrios undergo what for the last ten years has been known as bacteriolysis; and (3) that the serum of the animal acquires bacteriolytic and protective properties. Now with reference to this bacteriolytic serum, it had already been discovered that it could be deprived of its bacteriolytic power by moderate warming. But it was found that if the liquid so modified was introduced into the peritoneal cavity, its lytic power was promptly restored; whence it was concluded that the constituent of the serum which was destroyed by warming was in some form or other produced by contact with living cells.

I have ventured to repeat to you this story, with which no doubt every one present is familiar, because it contains what is essential to the understanding of the process of bacterial infection, and affords the data on which the distinction between the toxical and the bacterial form of the infective process can be founded. In the case we first considered, the encounter of the organism with a soluble toxine during an active immunisation, nothing more is required than that the two actions we have designated as severally *lethal* and *reactional* should be so opposed to each other that the effect of the former may be more or less balanced by the reaction due to the latter. When, as in natural infection, bacteria appear on the scene as carriers of infection, it is necessary that (if I may be permitted to employ teleological language) the process should adapt itself to the natural conditions of the infected organism. Pfeiffer's experiment, confirmed as it has since been by evidence derived from other sources, afforded ground for concluding that the power which the serum of animals immunised by his method possesses of dissolving the vibrio, is due to a constituent similar in nature to that discovered by Nuttall and Buchner several years before, and for the belief that in the bacteriolysis, which in Pfeiffer's experiment took place in the peritoneal cavity, two agents took part, the first of which was clearly a specific product of the collision between bacteria and living tissue—*i. e.* of the protective reaction of the

latter—the other pre-existing and non-specific, a normal constituent of living cells.

These conjectures would not have assumed the definite form that we are now able to assign to them, had it not been that about the same time another line of investigation was opened, which promises to be as fruitful as that of Pfeiffer. It was discovered that the toxic effects produced by *alien* blood-discs (*i. e.* blood-discs of an animal of a different species) when introduced into the living body correspond in many remarkable particulars with those of morbific bacteria. In this connection time will not permit me to do more than to mention the remarkable series of experiments by which Bordet[1] first demonstrated that the action of the hæmolytic serum thus obtained depends on two constituents, both of intra-cellular origin, one of which is specific and was designated by him "*substance sensibilisatrice,*" the other non-specific, the analogues of the two anti-bacterial products mentioned just now. The former is also called *immunisine,* a word which expresses perhaps better than any other its specific property of preparing the blood-disc or the bacterium, as the case may be, for the lytic action of the second constituent, called by Bordet the *alexine,* and by Ehrlich the *complement.* The great value of Bordet's experiment consisted in this—that it added clearness to the interpretation that had already been given of Pfeiffer's reaction, showing that the power which blood-discs and bacteria have in common of resisting the solvent (lytic) action of blood and tissues is annulled by the specific protective action called into existence by the penetration into the infected human or animal organism of alien blood-discs or of bacteria, as the case may be. I will ask you to take for granted the experimental evidence by which during the last few years these conclusions have been established and their meaning extended, in order that I may claim your attention to the recently conducted investigations relating to the nature and mode of action of hæmolysine at Copenhagen. The results of these inquiries have just appeared in the inaugural report of the Serum Institution, just opened at Copenhagen, which contains a series of most important papers, written in English. It is impossible to examine this volume without being impressed

[1] "Les Serums hémolytiques," 'Annales de l'Institut Pasteur,' 1900, vol. xiv, p. 257.

by the fact that the country that has given us our Queen offers us in our own language contributions to pathological science of an excellence which we shall find it difficult to equal. I can only refer to the two papers with which the volume opens. Two eminent men—Arrhenius, the well-known professor of physics at Stockholm, and Madsen, whose work on immunity is familiar to us—have, if I may so express myself, put their heads together for the solution of fundamental questions relating to hæmolysis. Before I endeavour to explain their scope I must remind you that the property of dissolving the coloured blood-corpuscles is possessed by many bacterial products, and particularly by the toxine of tetanus, and that it was discovered by Ehrlich some years ago that the hæmolytic constituent of this toxine was different from the "spastic," and that anti-lytic serum could be obtained by the ordinary process of immunisation. One of the most important of the Danish investigations relates to the question whether the neutralisation of this tetanolysine by anti-lysine conforms, as regards the physical conditions under which it takes place, to the process of neutralisation of an acid by a base. The answer to the question is in the affirmative.[1] For us the essential point is that the "lytic" process which takes so important a part in the defence of the organism against infection admits of exact investigation. At first sight this result might appear to be of little moment, for lytic action, although an essential concomitant of anti-lethal action, cannot be identified

[1] Arrhenius and Madsen, 'Physical Chemistry applied to Toxines and Antitoxines—Action of Antitoxine upon Toxine.' The purpose of this research is to compare the interaction of lysine and anti-lysine with similar interactions between substances of known molecular weight and constitution. The first result of the investigation was to show that when the process is conducted by successive addition of equal quantities of anti-lysine to tetano-lysine, the rate of diminution of hæmolytic power is very much greater at first than afterwards. By plotting the successive diminutions a curve was obtained, of which the characters express the time-relations of the process of neutralisation. This result having been arrived at, the next step was to compare this curve with a similar one obtained by the same method and representing a known physico-chemical process—namely, the neutralisation of a base by a weak acid. It was found that although in general the peculiarities in question do not present themselves in the combination of acid and base, there are certain cases in which, under special known conditions, the coincidence of the two curves is complete. This result affords reason for concluding that the combination of anti-lysine with lysine is a process within the reach of chemico-physical investigation.

with it. But in reality it is of the utmost significance, for the proof that the interaction of lysine and anti-lysine is of the same nature as chemical combination brings us one step nearer to the understanding of the fundamental antagonism between letha and anti-lethal action. The relation between the question of hæmolysis and that of the general action of toxine may be stated as follows:—We have two kinds of poisons concerned in the production of specific diseases or of morbid states:—toxines which act on particular cells, as, *e. g.*, the coloured blood-discs; toxines which act on the whole body. The former have been brought by the chemico-physical researches of Madsen and Arrhenius, for which those of Ehrlich paved the way, within the scope of exact scientific investigation. The latter are not as yet amenable to direct investigation of the same kind, but the close relation of these toxines to the others justifies the inference that the antagonism between them and their opponents may be dependent on chemical interaction.

I must now ask your attention to one more experiment relating to hæmolysis. The investigation in question is that published a short time ago by Dr. W. Bulloch.[1] Dr. Bulloch's method may be compared with Professor Pfeiffer's, with the substitution of blood-discs for cholera vibrios. It consists in the injection of repeated doses of the blood-discs of the ox into the peritoneal cavity of the rabbit, so as to render its blood more and more hæmolytic. Serum was collected at frequent intervals so as to observe the effect of the injections (1) on its hæmolytic power, and (2) on the number of leucocytes it contained. The hæmolytic power was estimated by first of all measuring *in vitro* the smallest quantity of the native serum which would take a standard quantity of ox blood-discs. From this datum Dr. Bulloch was able, by taking advantage of the fact that the specific immunisine was always in excess, to determine the variations of that constituent by adding an excess of lysine and then making a second measurement of the hæmolytic power of the mixture. In this way, although, of course, no measurement could be obtained of the quantities of the two constituents, the variations of hæmolytic activity during the period of infection could be estimated. Under different conditions the result of

[1] "Ueber die Beziehung zwischen Hämolysis und Bacteriolysis," 'Centralblatt für Bacteriologie,' vol. xxix, p. 732.

these experiments was most remarkable. Each treatment of the rabbit with ox blood-discs was followed after a period of incubation of several days by a rapid increase of the specific immunisine, this being ushered in by an increase in the number of leucocytes, particularly of the lymphocytes. In all the rabbits used in these experiments the serum obtained contained more of the specific constituent than was required to utilise the complement, and it was found that this excess was increased after every introduction of a fresh dose of the obnoxious blood-discs without any increase of the lysine, so that in order to obtain the full hæmolytic effect it was necessary to supply the lack of complement by the addition of serum from an intact animal.

The fact that the production and gradual augmentation of the specific property which must unquestionably be regarded as the essence of immunisation were preceded and accompanied by leucocytosis, recalls our attention to those lines of inquiry which relate to the part played by leucocytes in the processes we have been considering. I do not suppose that anyone questions that the effective constituents of bacteriolytic and hæmolytic serum are substances of cellular origin. As regards the lytic constituent, Metchnikoff and his school have abundantly shown that although both bacteriolysis and hæmolysis can take place without the direct intervention of leucocytes endowed with the faculty of phagocytosis, these structures take an important part in bacteriolysis. In connection with this subject, I may be permitted to remind you that during this year a communication was made to this Society by Professor Muir, of Glasgow, on the 'Reactions of Leucocyte-forming Tissues in Infections,' in which he conclusively showed that the leucocytosis which is observed in acute inflammations was associated with changes of a very remarkable kind in the marrow of bone. These changes, which he appropriately designates reactional, are characterised by the conversion of yellow into red marrow and the abundant proliferation of leucocyte-producing tissue. Professor Muir's observations further tend to show that this "reaction" is for the most part limited to the medullary tissue, neither spleen nor lymphatic glands taking part in it. I must not omit to mention that although no one has, so far as I know, investigated the subject so satisfactorily as Professor Muir, several pathologists, particularly Dr. Roger, of Paris, have described changes in the

marrow accompanying acute infective processes, of the same nature as those to which I have just referred.

What I have said may suffice to show that we have in these secondary infective processes in the tissues which produce blood-discs and leucocytes on the one hand, and in the lymphatic system on the other, a productive field of research which can be worked both chemically and experimentally—a field which is accessible to all who are thoroughly versed in histological methods. In this field what has already been done will afford indications of other lines of investigation of equal interest.

In conclusion, may I express the hope that the very imperfect outline of my subject I have been able to give may be found to be conformable not only to the experimental facts to which it has been possible to refer, but to the much more numerous and not less important ones which I have been compelled to omit? In dealing with scientific progress there is some risk in looking forward; but a certain amount of looking forward is not only permissible, but demanded. I confess myself wholly unable to forecast the discoveries of the next few years. There seem to me, however, to be two lines of advance for which two kinds of investigation are required. The one thing needful is to continue the investigation of the origin and nature of infective processes by experiments on animals and by the clinical study of the anatomical and functional changes which the specific infections produce in organs and tissues, and the protective reactions which are associated with them. But in addition to this, it is of great importance that the methods of physical chemistry should be applied to the interpretation of the experimental data. Of investigations of the first kind I have given a few instances out of many this evening. Of the second kind I could offer you no better example than the splendid research conducted by Madsen and Arrhenius.

REPORT.

SESSION 1902–1903.

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1. *The pathology of asthma.*[1]

By T. G. Brodie and W. E. Dixon.

(*From the Research Laboratories of the Royal Colleges of Physicians and Surgeons.*)

The term "asthma" in its original meaning was used with the significance with which we now employ dyspnœa, but its use has gradually become much more restricted. It is now usually limited to the affection known as bronchial or spasmodic asthma, and in this meaning only we use the word in the present paper.

Numerous theories have been advanced to explain the cause of the acute attack, the most important being classified by Osler in the following manner:

1. That it is due to a spasm of the bronchial muscles.
2. That it is caused by a swelling of the bronchial mucous membrane—fluctionary hyperæmia (Traube), vaso-motor turgescence (Weber), diffuse hyperæmic swelling (Clark).
3. That in many cases it is a special form of inflammation of the bronchioles, *bronchiolitis exudativa* (Curschmann).
4. That it is due to a reflex spasm of the inspiratory muscles, especially the diaphragm.

Of these theories the first is the one which, at the present time, is most generally supported, but there are still many who uphold the second and third views, or modified forms of them.

[1] Part of the expenses of this research have been defrayed by a grant from the Royal Society.

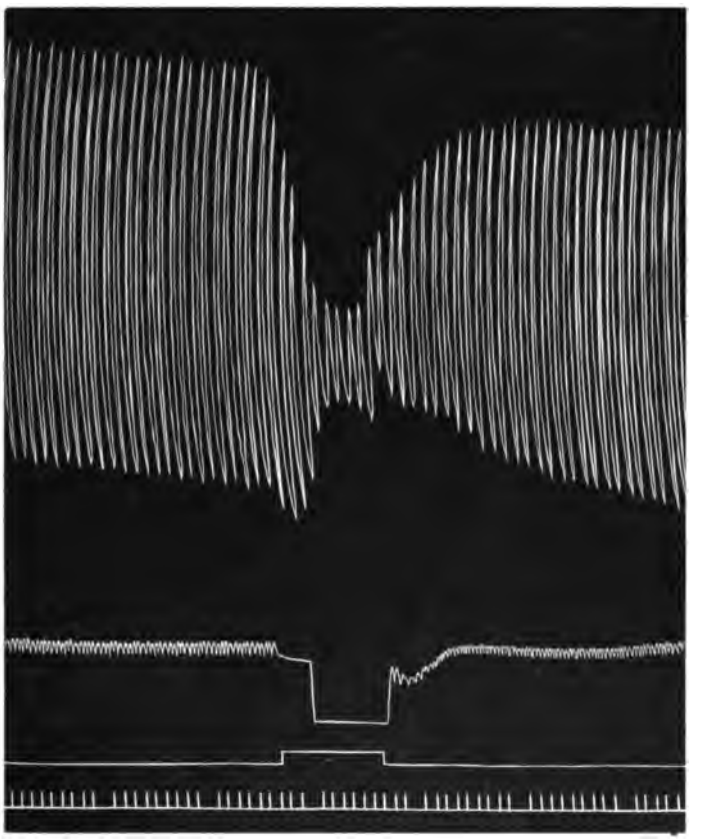
During the past three years we have studied the physiological behaviour of the bronchial muscles under many diverse conditions, and, as a general conclusion, have arrived at the view that a spasm of the bronchial muscles is in all instances the true cause underlying an acute attack of asthma. In this paper we give a brief account of the bearing which our experiments have upon the pathology of asthma, and the manner in which they can be utilised in explaining the symptoms and physical signs of an attack. Full details of the experiments up to the point at present reached are now being published in the 'Journal of Physiology.'

In most of our experiments the state of contraction of the bronchioles has been determined by recording the volume of air entering and leaving the lung during each respiratory act. This was generally effected by thoroughly exposing one lung by resection of several ribs, and then isolating one of the lobes, usually the lower lobe of the right lung, and enclosing it in an oncometer. As soon as the thorax was opened aëration was maintained by artificial respiration. This method possesses the advantage that throughout a long experiment the conditions of the supply of air to the trachea remain perfectly constant and under control. The oncometer is made air-tight by a stiff vaseline, and the changes in volume of the enclosed lobe recorded by connecting the oncometer to a bellows-recorder. The tracing obtained shows variations in the amount of blood contained in the lobe, as well as in the air waves, but the former are so much smaller than the latter that, as a rule, they introduce no difficulty in the interpretation to be placed upon the result. In most experiments the aortic blood-pressure was simultaneously recorded by a mercury manometer, thus enabling us at any time to estimate the general condition of the animal. We will, in the first place, give the results of our experiments upon the innervation of the muscles. It has previously been thoroughly established that the motor nerve to the bronchial muscles is the vagus. For a long time this conclusion was very much in question, but the experiments of MacGillavry,[1] Einthoven,[2] and Beer[3] have conclusively established it. They

[1] MacGillavry, 'Arch. Néerlandaises des Sciences,' 1877, p. 445.
[2] Einthoven, 'Pflüger's Arch.,' li, 1892, p. 367.
[3] Beer, 'Arch. f. (Anat. u.) Physiol.,' 1892, suppl., p. 101.

showed that the poor results obtained by previous observers were due to the methods they employed. The only satisfactory procedure is to prove that the movement of air into and out of the alveoli has been rendered either more difficult or more easy.

FIG. 1.[1]



Dog killed by pithing. Effect of stimulation of the right vagus (coil at 5) upon the air movements of the middle lobe of the right lung.

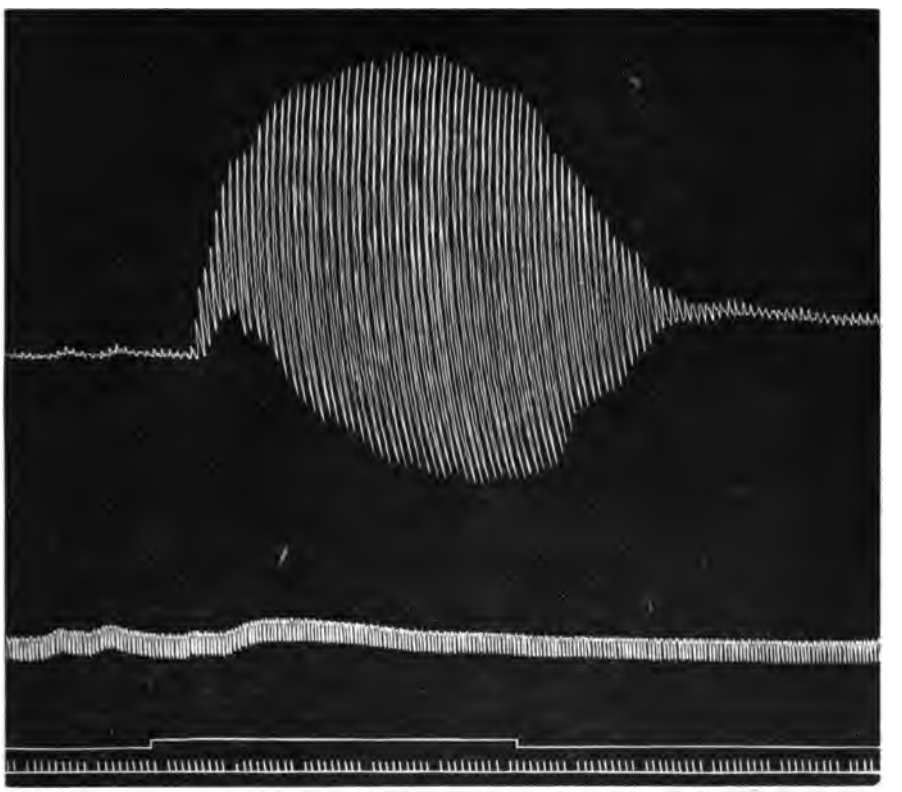
In our experiments this is attained by recording the volume of air entering at each inflation, the rise of air-pressure in the

[1] All the figures in this paper are to be read from left to right. The time record in all indicates seconds. The blood-pressure was recorded by a mercury manometer connected to the carotid. In the lung plethysmogram, a rise of the lever indicates increase in volume of the lobe.

trachea, and the total duration of that rise, being maintained quite constant for all inflations. A typical record of the result obtained is given in Fig. 1, which shows the effect of a short stimulation of the vagus upon a lobe of the right lung. The upper tracing is that of the lung-volume, and the lower the aortic-pressure curve. During the time indicated by the rise in the abscissa line the vagus was excited by induction shocks of such strength as to be just unpleasant when felt on the tongue. In the lung-volume tracing each rise represents the amount of air entering the lobe, and the fall, the amount of air leaving each time the lobe collapses. The effect of the stimulation of the vagus, therefore, is to rapidly cut down the amount of air entering and leaving the lobe. This is quickly produced, for in seven respirations the maximum decrease has been reached, and the amount of air which then entered was diminished to one fourth of the original volume; the heights of the air waves are 55 mm. before and 13 mm. after. The effect quickly passed off when the excitation was stopped. A result such as this can be repeated several times, but gradually becomes less and less pronounced, for the fibres are fairly easily fatigued to electrical stimulation. In this figure the lines passing through the apices and bases of the air waves of the lung tracing approach one another, the upper line being the one most affected. This means that the movement most restricted was that of inflation, a point we shall have to again refer to later. Similar reactions are to be obtained in the rabbit and cat, the other two animals upon which we have experimented, but in the latter animal the reaction is usually very different. The usual effect in the cat is a slight transient constriction, followed by a dilatation lasting until the excitation ceases, and about forty seconds later followed by a typical constriction. This reaction led us to conjecture that we were dealing with a twofold effect, one part tending to produce constriction, the other relaxation. We therefore proceeded to test for broncho-dilator fibres in the vagus, and soon succeeded in proving their presence. We had already shown that there is no tonus present in these muscles under normal conditions, and as, before it could be possible to show the action of such fibres, the muscles must be contracted, we, in the first place, induced a tonic contraction. This can be readily effected by the administration of muscarine or pilocar-

pine. Excitation of the vagus now produces dilatation of the bronchioles, an effect well seen in Fig. 2. In this experiment the air movements had been cut out completely by a dose of pilocarpine (3 mgrms.), and on now exciting the vagus the bronchioles relax and allow a considerable volume of air to enter

FIG. 2.



Cat, killed by pithing. Effect of excitation of the vagus (coil at 4 cm.), upon a lung in which the bronchioles had been constricted by a dose of pilocarpine. Figure reduced to two thirds.

and leave the lung with each respiratory act. Shortly after the excitation ceases the bronchioles again constrict under the influence of the drug. This reaction may be repeated a great number of times with precisely the same result on each occasion. Similar effects were also obtained in the dog and rabbit,

though apparently the dilator fibres are not quite so well developed in these animals as in the cat.

The bronchial muscles are therefore innervated by two sets of fibres, a constrictor and a dilator set, both of which run in the vagus. An examination of the sympathetic fibres leaving the upper thoracic cord for motor fibres to these muscles gave completely negative results.

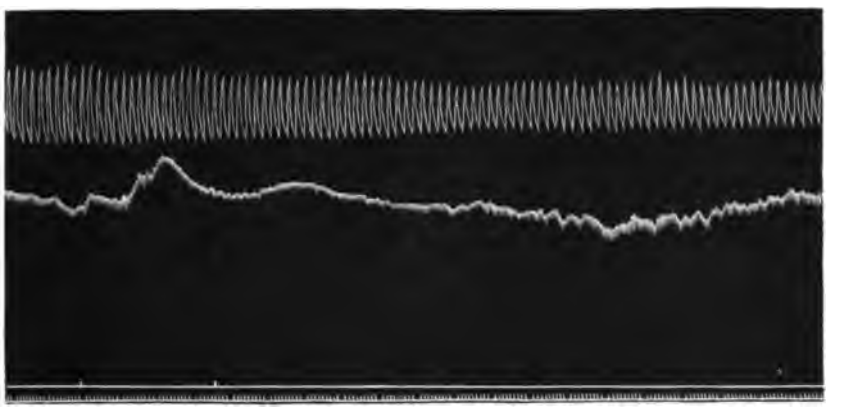
A considerable difficulty we met in all our early experiments, and which we only learnt to explain after much trouble, was due to the action of the anæsthetic. A large number of our early experiments gave negative results, which we ultimately found to be caused by the use of chloroform or ether as the anæsthetic. These, we found, paralysed the nerve-endings in the bronchial muscles, and we only succeeded in obtaining constant results on vagal stimulation when their use was reduced to a minimum. We therefore adopted the practice of anæsthetising the animal with the smallest necessary quantity of chloroform, and then destroying the medulla and brain. No further anæsthetic was then required.

It is necessary to mention this here because it explains the great difficulty we have experienced in obtaining reflex effects. Many observers have attempted to get reflex constriction of the bronchial muscles, but have only succeeded in a very partial degree. Thus, slight reflex constrictions have been described as following excitation of the sciatic, superior laryngeal, central end of the vagus, the cornea, and the nasal mucous membrane, but the tracings given in support of these statements are far from satisfactory. When working upon anæsthetised animals our attempts to produce these reflexes were almost entirely negative. It therefore became necessary to avoid the use of an anæsthetic altogether, or only to administer it for a very short time. As it was also necessary to keep the medulla uninjured, we worked upon decerebrate animals, but the conditions were still far from ideal, for the decerebration involves a rather lengthy operation under anæsthesia, and the injury produced in the majority of cases appears to set up a constant inhibitory effect upon the medullary centres. When working in this way, we therefore decerebrated the animal and then kept it for some three or four hours before proceeding with the experiment, in order to allow ample time

for recovery from the anæsthetic. But even under these conditions the results obtained have not proved as successful as we had hoped, and while giving the reflex effects we have at present succeeded in recording, we feel that there are still many undecided points to be worked out before we can understand the normal working of these centres. This is all the more unfortunate as the reflex mechanism unquestionably plays a most important part in the production of the acute asthmatic attack.

We have never succeeded in getting reflex constriction by excitation of a sensory cutaneous nerve, nor by excitation of the stomach or intestines, but we have at times recorded slight

FIG. 3.

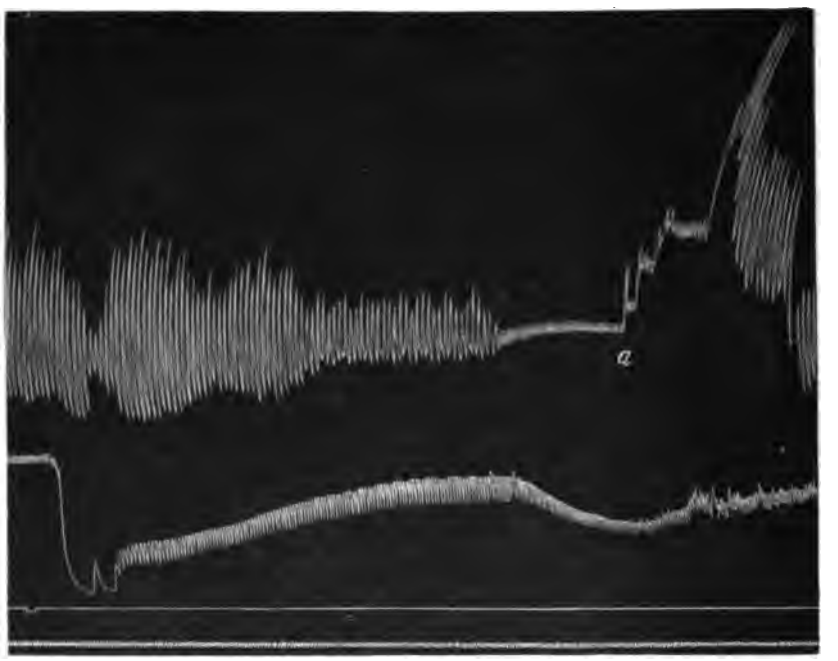


Dog. Decerebrate. Right lung-volume. Blood-pressure. Shows the effect of stimulating a point well back in the left nostril. Figure reduced to one third.

bronchial constriction on excitation of the central end of the vagus divided in the neck, or of the superior laryngeal. We never obtained any result from exciting the cornea. The most important reflex is, however, from the nasal mucous membrane. In all cases electrical, mechanical, or chemical excitation produces some effect. One of the best results is given in Fig. 3, in which the constriction produced results in a diminution of the volume of air entering the lung to one half its original volume. The tracing also illustrates well one other point, viz. the gradual onset of the constriction and its very prolonged course. Section of the vagus entirely abolishes the result, and

if the vagus be divided after the reflex constriction has been set up, the bronchioles at once relax. We have further observed that the upper and posterior part of the nasal septum is the best area from which to produce the reflex. From the experience gained from experiments of this class we feel quite sure that vigorous reflex effects are to be obtained, if we can find a method by which the centre can be isolated in a fairly normal state.

FIG. 4.

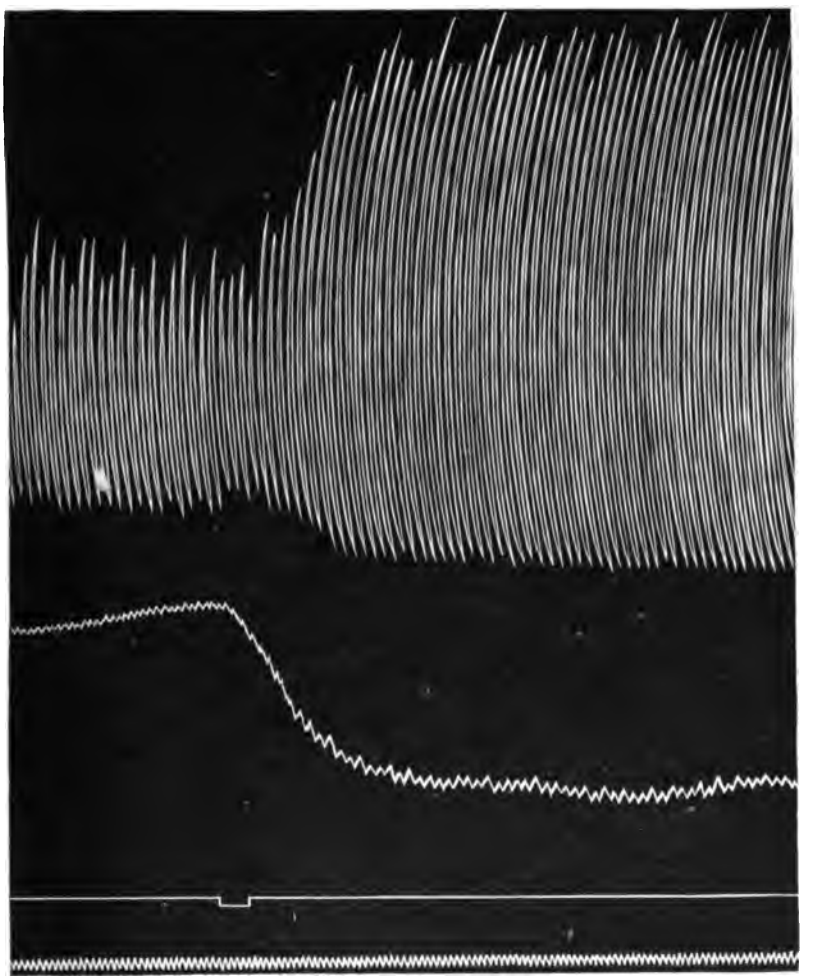


Cat. A.C.E. Injection of 0·001 grm. of muscarine sulphate. At the point marked "*a*" the force of inflation was increased. Figure reduced to one half.

We next come to the action of drugs upon these muscles. Muscarine, pilocarpine, physostigmine, and digitalin produce marked constriction by peripheral stimulation of the vagal endings. Gold salts, barium salts, and veratrine produce constriction by a direct action upon the muscle-fibres. Atropine, hyoscyamine, and hyoscine paralyse the vagal endings, and thus lead to dilatation if constriction is present. As examples of

these effects we give Figs. 4 and 5. Fig. 4 shows the result of injecting 1 mgrm. of muscarine, which is seen to produce a com-

FIG. 5.

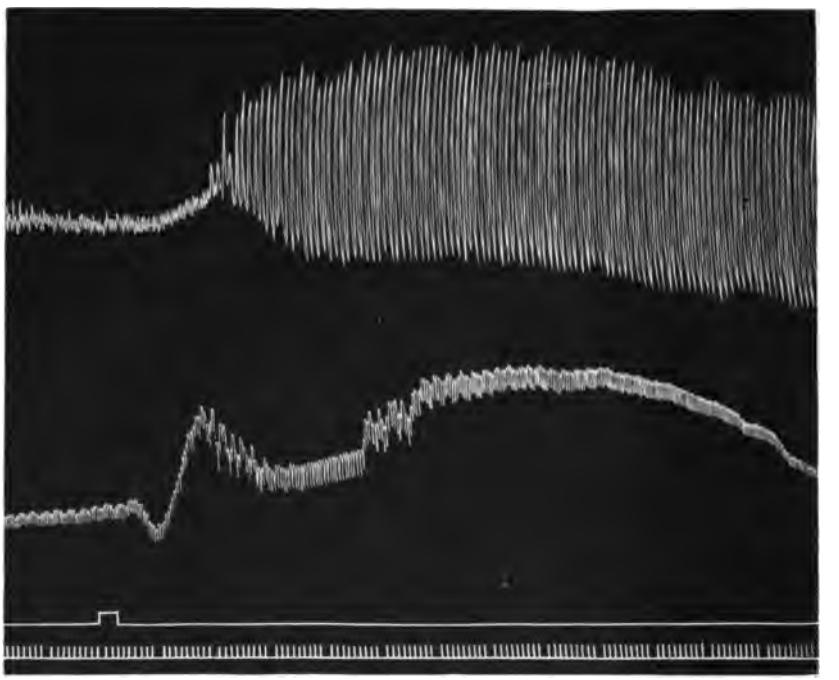


Cat. Lung-volume. Blood-pressure. Some bronchial tonus had previously been set up by an injection of pilocarpine nitrate. Shows the effect on the bronchioles of an injection of atropine sulphate into the jugular vein.

plete closure of the bronchioles to the ordinary pressure of inflation. It is also to be noted that slight over-distension of

the lobe is produced, a small quantity of air being permanently imprisoned in the lung. At the point marked "*a*" the force used to inflate the lungs was increased, and at once marked over-distension was produced, a point to which we return again presently. Fig. 5 shows the effect of administering atropine while the bronchioles are constricted by a previous dose of muscarine. Dilatation is at once produced.

FIG. 6.



Cat. A.C.E. Lung-volume. Blood-pressure. Shows the effect of an injection of the B.P. tincture of lobelia into the jugular vein. The animal had previously been given a small dose of pilocarpine, and the bronchioles were so constricted at the time of the tracing that no air was entering or leaving the lung. The zero of blood-pressure is 75 mm. below the abscissa line. Figure reduced three quarters.

Lobelia produces a most interesting result, especially of importance because of the place the drug occupies as a specific in the treatment of asthma. Fig. 6 shows the result of an intra-venous injection of the drug in an animal in which bronchial constriction had been produced by pilocarpine. It quickly produces relaxation, but, unlike the similar relaxation of atropine,

the effect is quite transitory, for in a short time the contraction returns, though it is not shown in this figure. Repeated injections of the drug can produce a series of such transitory effects, which in many particulars recall the broncho-dilatation produced by exciting the vagus in such animals.

Morphine also tends to produce relaxation when tonic constriction is present, but the dose required is relatively high, and the relaxation is never quite so marked as that following atropine or lobelia.

The action of carbonic acid is of very great importance. It acts chiefly, directly upon the medullary centre, producing a marked tonus, which may amount to a restriction of the air movements to one half their previous extent. In some instances we have also found the gas to exert a peripheral effect upon the nerves, for the tonus set up was not abolished, in all cases, by section of the vagus in the neck, although it was cut out by atropine.

We now come to the consideration of the bearing of these experiments upon asthma, and as a large number of our experiments have been concerned with the bronchial muscles, our main object will be to examine how far the theory of bronchial spasm can explain all the symptoms of asthma. The general history of an attack of asthma, its suddenness of onset, and rapid final recovery, indicate a nervous origin, and point to an excessive action of some physiological process carried to an abnormal degree. Practically all observers are agreed that the essential cause of the attack lies in a diminution of the lumen of the bronchioles, for the theory of diaphragmatic spasm has been shown to have been founded upon an erroneous interpretation of the symptoms and physical signs of an attack, and of the experimental data which appeared to support it. We need not further discuss it, and our issues, therefore, become narrowed to the three possible causes which can produce a diminution of the lumen of the bronchioles, viz. contraction of the bronchial muscles, acute congestion of the bronchial mucous membrane, or partial plugging of the bronchioles by secretion. A considerable proportion of cases of asthma are unattended by any expectoration, and the physical signs observed during an acute attack are much more those due to a restricted, but clear, lumen than to tubules containing a quantity of accumulated secretion.

The histories of asthmatic patients clearly indicate that the bronchitis is really secondary, a complication introduced by the highly abnormal state set up by the repeated attacks. For these and other reasons, to which we return presently, we think that the suggestion that the attack is due to accumulated secretion may be dismissed. We must therefore turn our attention to the other two possible causes, vascular engorgement and spasmodic muscular contraction. It has been argued that an acute vascular engorgement, quite similar to that which is well known to occur in the nasal mucous membrane, may affect the mucous membrane of the bronchioles, but we must point out that this is extremely unlikely, for the structure of the two membranes is most dissimilar. The nasal mucous membrane, especially over the inferior turbinate bone and lower nasal passages, is extremely vascular, and in many parts large venous plexuses are found encircled by bundles of muscular fibres, thus forming a sort of cavernous erectile tissue (Klein). The bronchial mucous membrane, on the other hand, is thin, and possesses what is, in comparison, a relatively insignificant blood-supply.

Of the points in favour of accepting the view that asthma is essentially a contraction of the bronchial muscles, the first undoubtedly is that the sudden onset and rapid disappearance of the attack exactly correspond with what we know to be the common course of a prolonged contraction of involuntary muscle. Again, a perfectly typical attack of asthma can be induced in an animal by giving it a small dose of muscarine. The dyspnœa and extended thorax are typically produced, and auscultation reveals the sibilant râles so characteristic of the disease. Moreover our experiments have proved that the whole of these lung symptoms in animals are due to the bronchial spasm. Practically no engorgement of the lungs is produced, and if only small doses of the drug are employed there is no excessive secretion into the bronchi and bronchioles. Moreover the attack thus induced may be instantaneously cut short by an injection of atropine, the recovery being complete, as is well seen from Fig. 5. In this instance it is impossible that any accumulation of secretion, or the presence of an œdema, could possibly have been the cause of the respiratory symptoms, as was at one time suggested by Grossmann. And, lastly, the conclusion is finally settled by the fact that excitation of the vagus

in these animals at once leads to recovery without modifying the heart or vascular system.

A further very strong argument in favour of this spasm theory is to be drawn from the study of the action of those drugs which have been empirically discovered to be of value in asthma. Foremost amongst these we may place chloroform and ether. We have already pointed out that it is almost impossible to produce a contraction of the bronchial muscles by stimulating the vagus in animals anæsthetised by either of these bodies. They act by paralysing the nerve-endings, which are exposed to concentrated doses of the vapour directly after its absorption through the mucous membrane. Just as stopping the anæsthetic will permit the production of a contraction by nerve excitation, so it is the common experience that if the dose of anæsthetic inhaled be too much reduced the symptoms again appear, although a remission from the attack had been gained by its use. We may consequently argue that it is probable that the attack is cut short because the drug has paralysed the vagal endings, which would imply that the constriction was originally produced by some excitation of those endings or by impulses passing down the vagi. That ether, especially, acts favourably in relieving the acute attack is distinctly against the view that the attack is due to a vascular change, for ether, as is well known, produces both hyperæmia of a mucous membrane and increased secretion from its glands, and should therefore tend, on this hypothesis, to make matters worse rather than better.

The next series of drugs we may consider are the alkaloids of the atropine series. All act similarly upon the bronchial muscles, producing complete relaxation when tonus is present, and all have attained high repute in the treatment of asthma. Atropine, in doses sufficient to completely paralyse the vagal endings, lowers the blood-pressure and dilates peripheral vessels. It thus tends to produce some engorgement of the mucous membrane, but, on the other hand, it would stop secretion. Its beneficial action in an acute attack, therefore, could only be explained on the vascular theory if there were some muscular mechanism in the bronchial mucous membrane which could be paralysed by atropine, and which when in activity produced marked congestion of the membrane. We have pointed out that no such mechanism is known to exist.

Morphine is another drug which has proved of the highest value in asthma, and, again, morphine we found to produce relaxation if tonus were present; but altogether apart from this action, morphine exerts a sedative action on all nervous centres, and this in itself could explain the beneficial action of the drug.

One further drug which it is necessary to consider is lobelia. The ethereal tincture of lobelia, when diluted, freed from ether, and then injected into an animal in which bronchial spasm has been produced by muscarine or pilocarpine, produces a most characteristic effect, viz. temporary relaxation (see Fig. 6, p. 26). The benefit only lasts a short time, but may be reproduced indefinitely by injecting further doses.

In the last place, there is one other drug which has been warmly recommended by several physicians as useful in asthma, but which we should at first sight have unhesitatingly condemned in strong terms, viz. pilocarpine. Pilocarpine in moderate doses produces typical bronchial constriction, but when testing the action of small doses we found that they produced no constriction. When experimenting with muscarine, a drug which in most of its physiological characteristics closely resembles pilocarpine, we frequently noted that it first produced relaxation before the constriction. In a few experiments we studied the action of minute doses of pilocarpine upon a lung in which the bronchioles were constricted by stimulating the vagus, and found that increased air movements into the lobe experimented upon resulted. This probably means dilatation of the bronchioles, but we cannot decisively state it to be this at present, because there is one other possible explanation, viz. that the increased expansion was due to bronchial constriction produced in the opposite lung. There is yet another possible explanation of any beneficial action of pilocarpine in asthma, viz. that the secretion copiously produced from the mucous surfaces by its use may for a time check or allay an abnormal process which had been operative from any of those surfaces.

No theory of asthma can be complete until it can adequately explain the whole of the symptoms of the acute attack. Perhaps the most important of all is the over-distension of the lung, which is so universal a symptom, and which has been the cause of the rejection by very many observers of the view we are now upholding. In the typical tracing we gave in Fig. 1

no over-distension is produced, but that is entirely a question of the procedure adopted for the experiment. If it is wished, one can in every experiment produce this over-distension by slightly altering the mode of artificial respiration; but we have not done so in our experiments because, though the production of an over-distension is the most striking feature of a tracing taken during the production of marked constriction, yet the method is not so sensitive for the purpose of showing small changes in the calibre of the bronchioles. We will therefore consider how the over-distension is to be produced in the first place in an exposed lung inflated rhythmically by an artificial respiration apparatus; and secondly, in a lung still within the intact thorax. We can then determine whether such results concur with the observed facts of the respiration and over-distension of the thorax in an asthmatic attack.

Over-distension occurring with bronchial constriction can be produced in the exposed lung by altering either of two factors in the artificial respiration, viz. (1) the force of inflation, or (2) the time allowed for deflation. Thus Fig. 7 illustrates the production of over-distension on excitation of the vagus. The effect was produced in this instance by shortening the time allowed for the lobe to empty itself in deflation. In the next place, if we refer again to Fig. 4 we see that at the point marked "*a*" in that figure over-distension is produced. This was caused by an increase in the pressure of the distending air, produced by partially closing the lateral orifice in the tracheal cannula, a change which became necessary because the animal was receiving no air into its lungs and was rapidly becoming asphyxiated. The explanation of the production of the over-distension in either of these two instances is not far to seek. The force producing inflation is relatively great (some 100 to 120 mm. of water at its maximum), but lasts only a very short time. The force emptying the lung, *i. e.* producing deflation, is relatively weak, for it is the elastic recoil of the distended alveoli and pulmonary tissue generally. It also becomes less the smaller the alveoli become, but, on the other hand, it is acting, as a rule, for a long time. Suppose, now, without in any way altering the force employed for inflation or its duration, we gradually decrease the time allowed for deflation, a stage is presently reached in which the recoil of the lung is not suffi-

ciently powerful to enable it to drive out as much air as had been driven in during inflation. In other words, the lung

Fig. 7.

of the bronchioles may be. Now suppose that in a lung in which this stage has just been reached the bronchioles are made to constrict. This introduces a further resistance to the air movements, which affects both inflation and deflation. But inflation is much more powerful than deflation; hence it will affect inflation less—a point we have abundantly proved by recording the rate of filling and emptying respectively. As a result, then, the lung is unable to empty as quickly as it is filled, and over-distension results, because no reserve of time is allowed for deflation.

A somewhat similar argument explains the production of over-distension when the distending force is increased. This results in greater filling of the alveoli, but the maximum alveolar pressure does not rise in proportion. Consequently, though the force of deflation is higher, it yet takes a longer time to empty the alveoli than before, and should the condition be carried a little farther it may not have had time to empty completely, and over-distension results. As a rule, with an ordinary res[illegible] pump and a normal lung this stage can never be r[illegible] cause [illegible] time is always a[illegible]ed by the mechan[illegible] lu[illegible] itself. In th[illegible] of our experim[illegible] with two an[illegible]ich had at some [illegible]n pleurisy [illegible]t of the lung had [illegible]racic wal[illegible] good [illegible]f care [illegible] one of th[illegible] se[illegible]s, and [illegible] indeed, ex[illegible]ver-di[illegible]ducibl[illegible] 7 is [illegible] rec[illegible] anim[illegible] othe[illegible] Phya[illegible] While, [illegible]ly [illegible] degree o[illegible] distending [illegible] occurs if th[illegible] explanation i[illegible] both to inflatio[illegible] ment of air is m[illegible] is produced [illegible] well whe[illegible]

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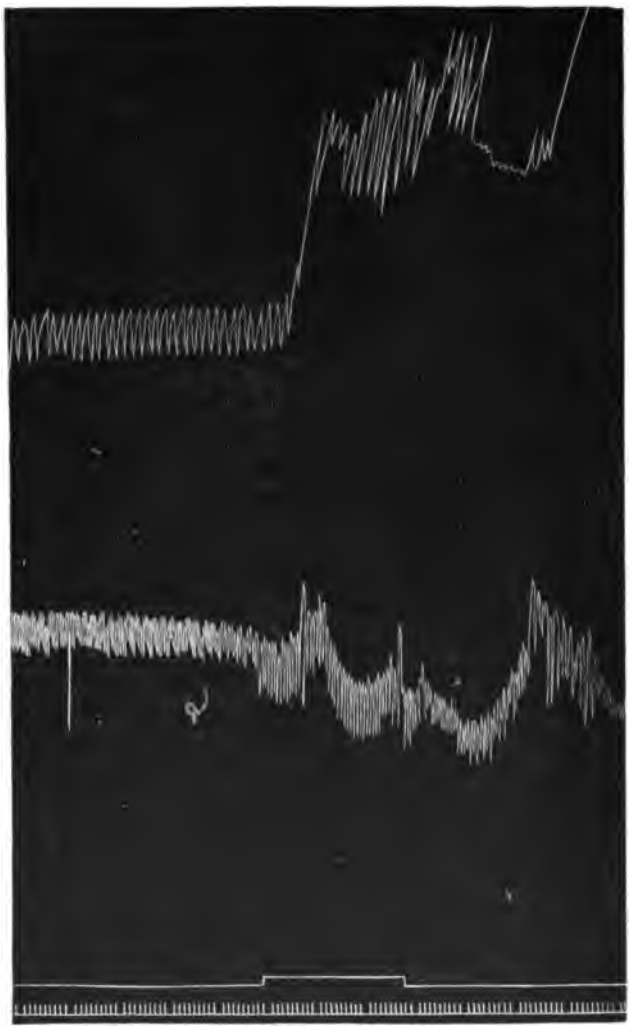
ciently powerful to enable it to drive out as much air as had been driven in during inflation. In other words, the lung

FIG. 7.



Cat. A.C.E. Right lobe in oncometer. Excitation of the right vagus by weak induction shocks (coil at 8 cm.) produces marked over-distension of the lobe.

begins to permanently over-distend—a condition which can be produced in any lung, no matter what the state of contraction

of the bronchioles may be. Now suppose that in a lung in which this stage has just been reached the bronchioles are made to constrict. This introduces a further resistance to the air movements, which affects both inflation and deflation. But inflation is much more powerful than deflation; hence it will affect inflation less—a point we have abundantly proved by recording the rate of filling and emptying respectively. As a result, then, the lung is unable to empty as quickly as it is filled, and over-distension results, because no reserve of time is allowed for deflation.

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The production of over-distension in the lungs while within the thorax is to be explained on exactly analogous lines.

Under normal conditions the force of inspiration is much greater than that of expiration, and acts to better advantage. By violent respiratory movements it is possible to increase the force both of inspiration and expiration very greatly. But the mechanics of the thorax permits a more marked increase of the power of inspiration than that of expiration:—the thorax is an inspiratory mechanism rather than an expiratory. Consequently, with normal respiration, marked constriction of the bronchioles is followed by over-distension. But in asthma, and in the asthmatic attack produced by muscarine, there is a yet more vital point to be observed. This is, that in both instances the effort is inspiratory. The patient exhibits violent inspiratory movements, whilst expiration is quiet and prolonged. In text-books of medicine sufficient stress is not laid upon this; indeed, many have described the type of respiration present during an attack of asthma as being characterised by increased force of the expiratory movements, and in nearly all instances the description is that the *respiration* is violent, not as it should be, that the *inspiration* is violent. The whole endeavour on the part of the patient is to get air in, not to drive it out. This was first clearly pointed out by Einthoven, who also showed that, though the condition leads to marked over-distension, yet, under the circumstances, it is the best possible thing for the patient, and chiefly because, if the force of expiration should have become excessive, some of that force will be transmitted to the outer surface of the already constricted bronchioles, and tend to make them collapse still further.

If asthma is due to contraction of the bronchial muscles, we must attempt to decide how that contraction is produced. Is it peripheral, central, or reflex? If peripheral, it might be due to a direct action upon the muscle-fibre or upon the nerve-fibre. As the attack generally involves the whole of both lungs, we could only assume that it was due to some chemical irritant uniformly distributed by the blood. The fact that atropine, chloroform, morphia, lobelia, etc., are all efficacious in relieving the attack tends to show that the action is *viâ* the nerves. The probability is that it is of central or reflex origin; but the other view, viz. that it might be of peripheral nervous origin, must also be considered. Mr. S. G. Shattock made the suggestion to us that possibly there was a local chemical irritant,

and that in that case it might be found in the sputum of an asthmatic patient. With his collaboration, we therefore performed a few experiments in which saline extracts from asthma sputum were injected intra-venously and sprayed into the air-passages. The results were completely negative. We also found that a solution of Charcot-Leyden crystals intra-venously injected was quite harmless.

We are not in a position to decide against the view of a peripheral cause in all attacks, but the facts that the whole of both lungs are usually involved, that the onset is sudden, and that only this particular set of muscle-fibres are involved, indicate a central origin, a supposition generally accepted by all, and strongly confirmed in that the patients in whom it is usually found are almost universally of the nervous type. If the attack is produced from the centre the acting cause may directly attack the centre itself, or a peripheral surface or organ. In this connection it is very important to note that carbonic acid in excess in the blood causes considerable activity of the centre in the medulla, probably by a direct action upon it. At any rate, the effect is not peripheral in most cases, for usually it is abolished by section of the vagi. The importance of this lies in that, in the paroxysm of an attack, carbonic acid is accumulated in the blood, and must therefore tend to still further increase and maintain the abnormal activity of the centre.

It is not probable that the cause of the attack is some direct irritation of the centre, otherwise we should expect to find some gross lesion of the centre, probably also involving neighbouring centres; and even if the exciting cause were a chemical irritant, analogy would lead us to expect some action upon other nerve centres. The probability therefore is, that the effect is produced reflexly, and it is in this direction that supporters of the muscular-spasm theory of asthma have sought for explanations of the disease. From the clinical side there is much evidence tending to bear this out. Thus in asthmatics it is most important to maintain the digestive tract in a normal state. An attack can with certainty be produced, in some patients, by an injudicious meal. Some have suggested that the sight alone of certain animals or objects can induce an attack, and there does not seem to be any question that the smell of certain animals (*e. g.* the cat) can produce an attack in some cases. With regard to the re-

spiratory tract, there are fair grounds for believing that in the predisposed an abnormal state of the bronchiolar, bronchial, tracheal, or laryngeal mucous membrane may induce, or at any rate favour, the onset of an attack. But the mucous membrane, which has most generally been acknowledged to play the most important part in asthma, is the nasal.

As already described, we have studied the reflex activities of this centre in a large number of experiments, but not with the success we had hoped. Still, our experience encourages us to persevere, for we can prove that the reflex excitability has always been considerably diminished in our experiments, so that those reflexes we have succeeded in obtaining must of necessity be much more active in a normal intact animal. The one reflex which has given us good results has been that from the nasal mucous membrane, and it has always shown the distinctive character of prolonged duration. Chemical, mechanical, and thermal irritants have all been effective. All this coincides well with very many facts that are known as to the causes predisposing to an attack of asthma. Odours, or minute changes in the atmosphere, which are perfectly imperceptible to the normal individual, can excite an attack in the asthmatic. Hay fever and asthma are well known to be closely connected in some causal relationship. Many complete cures of asthma have been effected by operative treatment of the nose. Dr. Greville MacDonald informs us that he finds those cases are the most favourable for operation in which sneezing is a prominent symptom, and that he has obtained the greatest success in cases in which there have been small growths on the inferior turbinate, which could be removed. The results recently recorded by Francis are so striking that they deserve the most attentive study. He states that nearly all cases of asthma may be permanently cured by cauterisation of a small area of the upper and posterior portion of the nasal septum. He expressly states that in many of his successful cases nothing abnormal was to be seen in the area cauterised. If, as Francis believes, the originating cause in practically all instances is some abnormal state of a part of the nasal mucous membrane, it would then be necessary to explain how unusual stimuli, arising from the stomach or lungs, could favour or even induce an attack. It may well be that the abnormal state of the nasal mucous membrane sets up such a de-

gree of hyper-excitability of the centre that any further stimulus, which under more normal conditions would excite no activity in the centre, can now suffice to produce the violent discharge originating the attack.

On the view that bronchial spasm is the one and only cause of asthma, the bronchitis always found in chronic asthmatics is the direct consequence of the abnormal states to which the lungs are subjected in the acute attacks. Many cases of asthma are known in which there is no bronchitis; indeed, the rule is that the latter develops after the asthma has obtained its hold. On the other hand, asthma is comparatively rare in cases of ordinary bronchitis, and the symptoms observed in the latter disease, even when there is but little secretion, are totally different from those of asthma, although we know that the mucous membrane is inflamed. In our opinion, as we have already stated, it is most unsafe to argue that, because the nasal mucous membrane can rapidly become turgid and swollen, and as rapidly recover, a similar thing can occur in the bronchi. Thus, in Clifford Allbutt's 'System of Medicine,' Goodhart writes: "It seems, therefore, a rational belief that what can be proved to exist in the upper air-passages—namely, a definite erection or turgidity of the nasal mucous membrane—may also take place lower down in the bronchial mucous surface, and, so doing, accomplish much of what we call spasmodic asthma." The onus lies with those who support this view to prove that there is such a vascular mechanism in the bronchial mucous surface which can permit of the production of such turgidity; the statements of histologists are directly opposed to it. We have in several experiments aimed at getting maximum turgidity of the mucous membrane by ligaturing or clamping the pulmonary vein issuing from a lobe, but we have never observed anything in the least comparable to the restricted air movements observed when the bronchioles are made to contract.

Our general conclusions, therefore, are that true bronchial asthma is in all cases a spasmodic contraction of the bronchial muscles; that if it follows or occurs in an acute attack of bronchitis, it has been reflexly produced either from the bronchial mucous membrane or from some other hyper-irritable mucous membrane, or possibly from the combined action of the

two abnormal surfaces acting on the medullary centre. The over-distension of the lung is the result of the bronchial spasm, and is produced because the action of filling the alveoli is always effected at a greater advantage than that of emptying, and that if extraordinary efforts at expiration are made, they do but serve to further impede the emptying of the distended lung. The state of the thorax and the modified respiratory movements are the direct consequence of the over-distension and the spasm. The increased violence of inspiration is due to the great force required to get air through the constricted bronchioles, and the so-called inspiratory spasm is the evidence of the over-distension. The chest does not collapse, and therefore the respiratory muscles and ribs cannot fall into the true expiratory position, in which movements of small extent result in considerable increase in capacity of the thorax. The violent movements observed consequently only result in a relatively small increase in capacity, and this in turn does not result in so large a fall in the alveolar pressure as would be produced by a similar volume increase in a less distended set of alveoli, because at the start the alveoli are well distended and filled with air practically at atmospheric pressure.

Having seen that reflex contraction of the alveoli can be produced, it necessarily follows that we should inquire—what is their significance, and what important function do they normally perform which has called them into existence? We have seen that the nasal reflex is the important one, and in considering its normal significance a study of the other reflexes obtainable from this surface is most important. The reflex effects which may be produced from the nasal mucous membrane are cardiac inhibition, dilatation of peripheral blood-vessels, arrest of respiration in the expiratory phase, spasmodic closure of the glottis, coughing, sneezing, and contraction of the bronchial muscles. All these are most easily produced, and their obvious meaning is to prevent the entrance of irritating substances, both particulate and molecular, into the respiratory tract. They can all be produced by chemical or mechanical excitation, and by blowing finely divided particles into the nostrils. Unquestionably one of the most effective results for the end in view is the contraction of the bronchial muscles, and this, therefore, appears to be the teleological meaning of the reflex in question. This, too,

fully explains the excessive sensitiveness of a large number of asthmatic patients to minute changes in the character of the air breathed, even though those changes are quite unappreciated by normal persons. *December 16th,* 1902.

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2. *Pathogenic varieties of* Bacillus coli *in ice creams.*

By E. Klein, F.R.S.

The *rôle* of the group of *Bacillus coli* in the causation of disease is becoming daily more recognised, particularly in reference to the presence of these microbes in foodstuffs, which thereby become endowed with the power of causing acute gastro-enteritis in the consumer. It has been proved that the particular variety of *B. coli* known as the Gaertner bacillus is the cause of acute gastro-enteritis in a number of outbreaks of this disease induced by the ingestion of certain meat foodstuffs. But it would not be justifiable to ascribe all occurrences of disease of this character to this particular variety—namely, the Gaertner bacillus,—nor would it be without a tendency to confusion to regard all microbes as belonging to the group of Gaertner bacillus which in rodents are capable of causing acute gastro-enteritis as part of a general hæmorrhagic septicæmia. In my experience there exist various microbes of the *coli* group, but which do not belong to the Gaertner group, which can cause, and moreover which have caused, acute gastro-enteritis; and I am fully in accord with most bacteriologists who have experience in this matter by excluding from the Gaertner group such microbic species as the bacillus of fowl cholera, the bacillus of swine plague, and the bacillus of swine fever, although these microbes are capable on ingestion of producing in rodents, in a considerable percentage of the experimental animals, acute gastro-enteritis as part of a general hæmorrhagic septicæmia. In respect of microbes which certainly do not belong to the Gaertner group, and which have caused acute enteritis in human beings, I may be permitted to refer to two notable out-

breaks of meat poisonings which have been described in the 'Reports of the Medical Officer of the Local Government Board.' The first—the Carlisle outbreak—is described in the 'Report' for 1889. Here it was pork and gravy stock which had been at fault. From the same establishment and from the same stock from which the poisonous pies had been derived, pork and gravy stock proved capable of causing, by feeding of mice, acute gastro-enteritis and death in a large percentage of the animals. From these animals a microbe was isolated which on inoculation and by feeding of further animals proved highly virulent. This microbe certainly did not belong to the Gaertner group, since its growth caused slow liquefaction of gelatine. Another outbreak—the Portsmouth meat-pie poisoning—was published in the 'Report of the Medical Officer of the Local Government Board' in 1890, p. 249. In this outbreak the poisonous nature of the meat pie was fully confirmed by experiments of feeding mice with the meat pie; the microbe isolated both from the pie and the experimental animals was a virulent *B. coli*, which certainly does not belong to the Gaertner group. Now it may not be unnecessary if I here restate the characters which bacteriologists assign to the variety of *B. coli* known and considered as the "Gaertner bacillus." The Gaertner bacillus in respect of the nature and aspect of the colonies in the plate, in streak, stab, and shake culture in gelatine and agar, in its growth in carbolised broth, in its general morphology, in its inability to stain by Gram, in its giving positive neutral red test, admittedly belongs to the group of *B. coli*, but it differs from the typical *B. coli communis* in the following respects:—*B. Gaertner* does not clot milk; *B. Gaertner* forms alkali (litmus milk and litmus broth becoming gradually blue); *B. Gaertner* ferments, produces CO_2 gas from glucose like *B. coli communis*, but *B. Gaertner* does not ferment lactose (*B. coli communis* does so); *B. Gaertner* does not form indol in broth; *B. Gaertner* is multiflagellated similar to, though not identical with, the *Bacillus typhosus*. There are, therefore, a number of characters, morphological and cultural, by which the *B. Gaertner* is readily distinguished. To this must be added also that *B. Gaertner* is virulent to rodents subcutaneously injected even in minute doses, and in larger doses it is capable sometimes of causing general infection also by ingestion. On the other hand,

a microbe which produces acid in cultivation, which curdles milk, which ferments both glucose and lactose, which is not multiflagellated, which produces indol in broth culture, cannot claim to be considered as *B. Gaertner,* but must be content with a place in the group of *B. coli communis.* Now a microbic species of this kind, but possessing highly virulent character, I have isolated from certain samples of ice creams, which I shall describe in detail presently. I may at once say that the culture of this microbe caused, on inoculation of minute doses into rodents, general hæmorrhagic septicæmia, including acute gastro-enteritis and peritonitis, and death within twenty-four to forty hours. Ingestion of culture caused illness of the majority and death of a proportion of the animals experimented on. On *post-mortem* examination of the latter acute and severe gastro-enteritis and peritonitis were found, the whole of the small intestine being deeply congested, relaxed, filled, and distended by sanguineous masses. I show under the microscope a specimen of the sanguineous exudation filling the subcutaneous and muscular tissues of the abdomen and chest of an animal that died within twenty hours after subcutaneous injection of a minute quantity of a particular sample of ice cream. Culture by plates proved that the bacilli which you see almost densely filling the exudation belong to one and the same species; and further inoculations with the exudation (one or two drops for a half-grown guinea-pig) caused the same fatal disease with the same distribution of the microbe in the dead body. Not only was the subcutaneous tissue full of the sanguineous exudation crowded with the bacilli, but also the lungs, the pleural and pericardial cavities, the peritoneum and the intestines. A second specimen shown under the microscope is a stained film of peritoneal exudation of a guinea-pig which had died within twenty-four hours from acute gastro-enteritis after feeding with a gelatine culture of the bacillus. Plate culture made with this peritoneal exudation proved the bacilli to belong to one and the same species—namely, the species used for the feeding. The microbe in question belongs undoubtedly to the *coli* group; in morphological and cultural respects it is closely related to the typical *Bacillus coli communis,* from which it differs in certain respects; it is more motile in the hanging drop than the *B. coli communis,* although it possesses only one to five flagella. Like

B. coli, it ferments glucose and lactose, it curdles milk, produces acid, and doubtful or slight indol (?); in broth culture it gives positive results in neutral red test. On potato it forms a colourless thin film, and, as already mentioned, is highly pathogenic, both by subcutaneous injection of small doses, and also by ingestion of gelatine culture. I produce here cultures of *B. coli communis*, of *B. Gaertner*, and of our pathogenic ice-cream bacillus, to show their chief points of cultural differences and resemblances. The sources from which the above microbe was obtained were, as mentioned already, samples of ice creams. Dr. Collingridge,[1] the Medical Officer of Heath for the City of London, had been informed by the medical officer of the General Post Office that two telegraph boys (afterwards it appeared that altogether thirteen suspicious cases had come to the notice of the medical officer of the General Post Office) had been taken ill with what appeared to be acute gastro-enteritis, believed to be due to poisoning by ice cream bought at an Italian shop in Aldersgate Street. Dr. Collingridge therefore sent to me, for analysis and experiment, samples of ice cream that were bought at these shops. Both samples were, indeed, found to have poisonous properties, inasmuch as the injection of ½ c.c. to 1 c.c. subcutaneously into half-grown to full-grown guinea-pigs caused extensive inflammation and gangrene of the subcutaneous and muscular tissues, as also intensive inflammation of the peritoneum, of the stomach and intestine. In the exudation anaërobic microbes, as also, and in great abundance, the highly virulent variety of *B. coli*, were met with. On further transmission by subcutaneous injection of a drop or two of the sanguineous exudation, this particular species was obtained almost in pure culture. Not only in those samples, but in several other samples of ice cream sent to me for analysis by Dr. Collingridge, was this or some very similar highly virulent variety of *B. coli* met with; and I would particularly refer to a number of samples taken at different dates from different shops, but all supplied by one and the same maker. They all proved of the same poisonous nature, and this character persisted until the maker abandoned the highly insanitary conditions then prevailing on his premises, and complied with the suggestions and require-

[1] 'Report of the Medical Officer of Health of the City of London,' September 29th, 1902, p. 120.

ments of the medical officer. As soon as this change took place the ice creams became harmless; injection of 1 c.c. of the material into small guinea-pigs failed to exert any pathogenic action. The materials from which the ices were made were themselves found to be harmless, and therefore the poisonous nature of the ice creams must have been due to admixtures by the extremely insanitary local conditions under which the ices were made, the uncleanliness of the manipulating persons, and the storing and keeping of the "stock" of ice creams in filthy places. This latter malpractice is particularly favoured by some makers—namely, the ingredients are mixed so as to form a common "stock." This is used for freezing in such quantities only as are likely to be required for sale that day; the rest is kept in a dirty place for future freezing and sale. No better confirmation, I think, of the correctness of the recently passed law (as regards the manufacture and sale of ice creams) could be desired. *November 4th,* 1902.

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3. *On the bacterial flora of London air.*

By F. W. Andrewes.

I have recently had occasion to make a number of determinations of the micro-organisms in London air, both quantitatively and qualitatively. The samples were taken in a number of different streets, open places, and parks in the West End and in the City. It may be of interest to this Society to see the apparatus employed, which in my hands gave very consistent results, and also a number of the cultures obtained, which illustrate fairly well the bacterial flora of the air of London. The method used was that of Frankland, viz. the aspiration of a known volume of air through a plug of powdered glass-wool and sugar, plate cultivations being subsequently made from the plugs. The aspiration was carried out with a large brass syringe, holding 420 c.c., and fitted with a two-way nozzle and tap, so that a number of syringefuls could be aspirated without disconnecting the apparatus. In order to obtain good results with this apparatus a number of small details require attention.

In making the plugs the glass-wool should not be too finely pounded, and it should be mixed with about one fifth its bulk of very finely powdered loaf sugar. This gives a very coherent plug, not liable to disintegrate, and readily forced out from the tube as a solid mass, which, in the melted culture medium, breaks up uniformly. The plugs are fitted in ordinary glass tubes, about five inches long and a quarter of an inch in internal diameter. The powder is introduced into these and compressed from each end with solid glass rammers, fitting the internal calibre of the tube. Each plug requires testing by forcible aspiration through it, to make sure of its coherence. If it stands the strain the ends of the tube are plugged with cotton wool, and the whole sterilised in the hot-air chamber for an hour or two. The temperature should not rise above 140° or 150° C., lest the sugar be charred. I tested the efficacy of such plugs in retaining the whole of the bacteria in the aspirated air, by introducing in the proximal end of the tube an additional plug of cotton wool, through which the air had to pass immediately after traversing the glass and sugar mixture. This cotton-wool plug was always tested by cultivation, and was commonly found sterile, even when the glass-wool plug yielded over 100 colonies of bacteria and moulds.

The amount of air selected for each aspiration was five litres, *i. e.* eleven and three-quarter syringefuls. It took about eight minutes to aspirate this volume. The *modus operandi* was as follows:—Two brass clips to hold the tubes, furnished with rubber suckers, were wetted and fixed close together on a window, smooth wall, or other convenient surface. In open spaces, such as parks, they were fixed on a glass plate laid horizontally on the ground, or on a box. The tube, with its plug, was now taken from its sterile bottle, care being taken not to touch the ends. One end was connected with the syringe by four feet of rubber tubing, and the tube was fixed in the brass clips. The cotton wool was removed with sterile forceps from the free end, and placed in a sterile dish, to be similarly replaced at the end of the aspiration. The length of rubber tubing enabled the operator to stand some way off while conducting the aspiration, and, naturally, on the leeward side. When the operation was completed and the cotton wool replaced, the tube was labelled and conveyed to the laboratory in its sterile bottle.

The cultures were made as follows :—A Petri dish was warmed, and a melted gelatine or agar-agar tube poured into it. The tube was removed from its bottle, and the inner of the two cotton-wool plugs at its proximal end placed in a broth tube for incubation, to see if it had remained sterile. The distal cotton-wool plug having been also removed, and both ends of the tube having been passed through the flame of a Bunsen burner, the glass and sugar plug was now forced out with a sterilised glass rod into the Petri dish. It could easily be disintegrated by gentle agitation, and distributed equably through the medium. The glass particles caused a uniform turbidity, which in no way interfered with the subsequent enumeration of the colonies. I made all my observations in pairs, making an agar-agar plate to be incubated at 37° C., and a gelatine plate to be incubated at 20° C. The latter was used for the enumeration of the total number of organisms, but it was hoped, by a comparison of the two, to find out something of the ratio between the organisms capable of growing at blood heat and the psychrophile organisms, which might serve as an index of human contamination. I cannot say that the results fulfilled this hope, but the matter requires fuller investigation. At blood heat the sarcinæ proved the predominating organisms, and I do not know how far they can be taken as of human origin.

In determining the total number of organisms, I found it necessary to establish an arbitrary time limit for counting the colonies which arose, and I was led to fix this at four days. The number of new colonies which first appeared after this limit was not very large, and was outweighed by the fact that rapidly growing moulds, such as *Penicillium glaucum*, sporulated and gave rise to secondary colonies, if one waited too long. Moreover my object was the comparison of different samples of air, which could be attained perfectly well by counting all plates at a fixed date. In counting the colonies, I divided the plates into sectors and made a map of every plate, using a hand lens, supplemented by a low power of the microscope. Having counted the colonies, subcultures were made in order to determine their species. Where the number was large, subcultures were made from every colony in one half, or one quarter, of the plate, and from the remaining area only from such colonies as appeared manifestly diverse from the rest.

The method described led, as I have said, to very fairly consistent results, and I believe it to be as good a method as we have at our command for determining the gross bacterial contamination of different samples of air. It has, however, certain defects. I found on subculture that a certain proportion of the colonies arising were in reality composite colonies, consisting of two, or sometimes even three species, and I imagine that this is due to the fact that a given dust-particle may contain more than one species of micro-organism. The error introduced is not large, but it exists as a factor in the numerical estimation of the bacteria in the air. It is further obvious that certain micro-organisms—and these of much importance—would escape recognition. The tubercle bacillus is one, and there are other delicate species, such as the streptococci and the pneumococcus, which might easily fail to grow. I only once found a streptococcus in my cultures, though streptococcal contamination of air must be a common thing, considering that streptococci are the commonest mouth organisms. Anaërobes, again, would not be recognised. I twice conducted special experiments to determine their presence, aspirating ten litres of air and incubating the plug anaërobically in glucose broth, but with negative result.

The determination of the species of bacteria found was a long and troublesome task; indeed, in many cases an impossible one. The colonies were subcultivated on various media, and examined microscopically in the fresh condition and stained. Many were identified at once, but in many the names affixed are only provisional, while, in not a few cases, I could find no description in any of the text-books at all corresponding to the organisms found.

The difficulties that beset the subject are of two kinds. Very little attention has hitherto been paid to the organisms of the air. Their presence is more or less accidental, and they do not grow and multiply there. It has not yet been shown that they are of much practical importance, though I am not sure that their closer study might not reveal relations which might be of value as an index of organic contamination. But so far they are imperfectly known and described—so imperfectly that often one has not the data for identification. Another difficulty lies in the extreme variability of many common air bacteria. The sarcinæ are a case in point. The assumption of the typical sarcina form

is inconstant; I repeatedly passed an organism as a staphylococcus, to find, on re-examining an old culture, that it had now assumed the form of a sarcina. One species grew beautifully in hay infusion as a sarcina, but on no other medium would form even tetrads. The liquefaction or non-liquefaction of gelatine is of no value whatever as a specific character amongst sarcinæ. The variations in tint from white, through yellow, to orange, are of infinite diversity. I subcultured more than a hundred sarcina colonies, and ultimately grouped them into three species, *Sarcina alba*, *S. flava*, and *S. lutea*, but I have still grave doubts as to how many species were really present. I am inclined to agree with Lehmann that each sarcina species has its first cousin amongst the cocci which form no packets, and that no hard and fast line can be drawn between the two.

Next to the sarcinæ in frequency come the various staphylococci. Of these, the commonest are the two species I have labelled *Staphylococcus cereus albus* and *flavus*, forming a smooth waxy growth on gelatine, which liquefies slowly, or not at all, and is usually stained a faint claret colour by some pigment emanating from the growth. These species are very closely allied to the sarcinæ, except in the formation of packets. *Staphylococcus pyogenes albus*, and its slowly liquefying form *S. epidermidis albus*, were met with only a few times; *Micrococcus cremoides* and *M. candicans* much more frequently. One or two interesting motile cocci were found, including *Micrococcus citreus agilis* and *Diplococcus luteus*. Some of the cocci were beautifully chromogenic, especially *Micrococcus aurantiacus* and *M. roseus*.

Numerically I found the bacilli to fall far short of the cocci, but the number of species found was large. The commonest was a large stout psychrophile white bacillus, chemically inert, which I identify with *B. lactis innocuus* of Kruse; in old cultures the gelatine was stained brown. Some of the bacilli were chromogenic, notably *B. helvolus*, *B. latericius*, *B. luteus*, and the beautiful *B. erythromyxa*, once met with. *B. carneus* was twice found, and *B. pyocyaneus* once. Sporing bacilli were sometimes present, *B. subtilis*, *B. mesentericus fuscus*, *vulgatus*, and *ruber*, and others which I could not determine. Diphtheroid bacilli occurred many times—*B. xerosis*, and others more closely allied to the diphtheria bacillus. The one which came nearest to the diph-

theria bacillus gave good polar granules with Neisser's stain, but proved non-pathogenic.

Yeasts were commonly found, but, of five species, only one proved capable of fermenting sugar. Streptothrices were by no means rare, and were referred to three or four species. Moulds, of course, formed a large proportion of the total organisms found. *Penicillium glaucum* was the commonest, and was rarely absent from a plate. The various species of aspergillus were also commonly met with. In addition to these were a number of moulds whose very genus I have been unable to determine.

One fact struck me very forcibly in these observations, viz. the remarkable chemical inertness of the common air bacteria. Not only was no truly pathogenic form found, but no single species which formed gas in glucose gelatine shake cultures, and hardly one which coagulated milk or formed acid.

November 4th, 1902.

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4. *The effect of certain metallic salts upon the growth of micro-organisms.*

By David Nabarro.

The experiments described in this paper were begun some two and a half years ago, primarily with a view to find, if possible, some medium upon which the *B. typhosus* would grow while the *B. coli communis* would not, or a medium in which a distinctive colour-reaction might be produced by the growth of the *B. typhosus* and not by the *B. coli*. I may say at the outset that I failed in the quest on which I had embarked, but a few interesting facts were established which I have thought worth recording.

The method adopted was to add a minute quantity of salts of nickel or copper to ordinary culture media. Originally it was intended to try the effect of cobalt salts as well as the others, but I have been unable to continue the investigation owing to the pressure of other work. The reason for selecting the salts of these particular metals was that they are beautifully coloured,

nickel salts being green, cobalt red, and copper blue. It was thought that possibly the growth of the *B. typhosus* might give rise to some change in colour of the medium, or in the case of a broth culture might produce a coloured deposit or precipitate. A further reason why copper was chosen was that chemical bodies of the acetylene series yield solid crystalline compounds by the action of ammoniacal solutions of copper salts. Most of these copper compounds are brightly coloured, and it was just possible that these micro-organisms during their growth might form similar substances which would combine with the copper. The salts used were nickel chloride, nickel sulphate, and copper sulphate. Half a gramme of the salt was added to a litre of nutrient broth prepared from Liebig's extract and Witte's peptone, and rendered slightly alkaline with Na_2CO_3. The nickel or copper salt was added to the broth before the final sterilisation. In the case of nickel no precipitate was produced, and the resulting medium was slightly alkaline and of a greenish colour. On the addition of ammonium sulphide a slight black precipitate of nickel sulphide was formed. When copper sulphate was added to the clear broth, however, a precipitate was formed. This was filtered off and the resulting fluid tested for the presence of copper. It was of a greenish colour, and on the addition of H_2S a dark brown coloration was produced, but no precipitate. The majority of the original ½ gramme of the salt used had evidently precipitated when added to the broth, so that while the percentage of Ni in the "nickel" media may be taken as 0·05—that is to say, 1 part in 2000,—the percentage of copper in the "copper sulphate" media was much less, but its exact amount cannot be stated. The effect produced by the addition of these salts to the culture media was studied in the case of the following micro-organisms:—*B. typhosus, B. coli communis, Staphylococcus pyogenes aureus, Streptococcus, B. pyocyaneus, B. prodigiosus, B. anthracis, Proteus vulgaris, Sarcina lutea,* and *B. subtilis.*

As the experiments were carried out primarily with a view to find, if possible, some distinctive culture media for the *B. typhosus,* I shall begin by giving an account of the behaviour of that micro-organism in the nickel and copper media, putting in close juxtaposition the results obtained with the *B. coli communis* for the purposes of comparison.

B. typhosus.—A "nickel-chloride" broth was inoculated from a typhoid culture on agar, and incubated at 37° C. In twenty-four hours very slight turbidity was seen in the broth. A hanging-drop preparation showed some organisms, but they were feebly, if at all, motile. The growth of the *Bacillus typhosus* had been inhibited by the nickel, but the organisms were still alive, as was shown by making a subculture on ordinary agar. Some small colonies, but not very many, developed on the agar in twenty-four hours.

The nickel broth on the second day after inoculation showed no more turbidity than was present on the first day. On the fifth day the broth presented the same appearance, the bacillus having evidently not multiplied at all. It was again tested by subculturing on ordinary agar to see if it were still alive. There was no sign of growth on the agar in twenty-four hours, but on the third day a single colony, about one fifth of an inch in diameter, had grown.

The original nickel broth was examined again on the eighth day after inoculation. There was no turbidity, but a slight deposit, and on testing its vitality by sowing on ordinary agar it was found to be dead.

B. coli.—Comparative experiments with the *B. coli* gave the following results:—The nickel-chloride broth on the first day showed very slight, if any, turbidity. In hanging drop the organisms were scanty and non-motile. Subcultures on ordinary agar grew in twenty-four hours, the colonies being larger and more expansive than in the corresponding typhoid tube.

On the second day the nickel-chloride broth of *coli* was practically clear, as it was also on the fifth day. On that day it was again subcultured on to agar to see if it were alive, and, as was the case with the *B. typhosus*, no growth occurred in the first twenty-four hours. On the third day, however, a single large colony (quarter-inch in diameter) had grown, and by the next day it had spread well over the surface of the medium. The single colony, which developed under similar conditions in the case of the typhoid bacillus, did not increase subsequently in size, as did the *coli* colony. The original *coli* nickel broth on the eighth day showed a slight deposit, and on subculturing on to agar was found to be dead.

These effects of nickel chloride on the *B. typhosus* and the *B. coli* in broth may be thus summarised:

1. The growth of the organisms was inhibited at once.

2. The organisms were gradually killed, and by the eighth day all were apparently dead.

3. Before being killed they were modified in some way, so that when subcultured on ordinary agar (as was done on the fifth day) no growth appeared on the agar until the third day in each case; then only one colony developed in each tube, but the *coli* colony spread in a characteristic fashion, while the typhoid colony did not increase in size after its appearance.

The next experiment was made with nickel-chloride agar. This medium was inoculated from a typhoid culture on ordinary agar, but no growth occurred in eight days. The tube was then re-inoculated, when a slight growth appeared on the first day and increased but slowly up to the eleventh day. In the case of nickel-chloride agar inoculated with the *B. coli*, a typical growth occurred on the first day, which increased on the next day, but not subsequently. The effect of adding nickel chloride to agar media was therefore not nearly so pronounced as in the case of broth. The growth of the typhoid was inhibited to a certain extent, while that of the *coli* was hardly affected.

Next the growth of the typhoid and *coli* organisms was studied in nickel-chloride gelatine media.

The *B. typhosus* was inoculated from agar into a nickel-chloride gelatine stab. In one day at 22° C. there was very slight growth, mainly on the surface. On the second day it had increased a little, and there was also growth along the track of the needle. At the end of eleven and twenty-eight days there was a good growth in the depths of the stab line. No liquefaction of the gelatine or formation of gas was observed. This experiment was repeated with very similar results. It was noted that on the eleventh day a fairly good crop of minute discrete colonies was visible along the stab line, but much less than in a similar culture of *coli* only six days old. The *B. coli* grown under similar conditions showed a growth on the surface in one day. In eleven and twenty-eight days there was a large expansive growth on the surface and a good growth in the depths. No gas formation or liquefaction present.

In a nickel-chloride gelatine "shake" preparation the *B.*

typhosus showed no obvious signs of growth in seven days, a control ordinary gelatine shake showing a good growth in that time, as well as some opalescence near the surface of the medium. On the twelfth and twenty-fourth days the nickel tube showed a slight growth throughout the medium, but no opalescence near the surface. On those days the control tube showed marked signs of growth in the depths and opalescence above. The *B. coli,* under similar conditions, grew practically as well as in the control tube of ordinary gelatine. Quite as much gas was produced as in the control tube, and almost as much opalescence.

Inoculated on nickel-chloride gelatine slope-tubes, the *B. typhosus* gave a very slight growth, increasing up to the third day, while the *B. coli* gave a good growth by the sixth day.

To summarise, then: nickel chloride added to gelatine media very materially inhibits the development of the *B. typhosus,* while it has only a slight retarding effect upon the growth of the *B. coli,* and no effect upon its production of gas.

The next series of experiments was made with nickel-sulphate media.

The typhoid bacillus, inoculated into nickel-sulphate broth, showed no visible growth or turbidity in twenty-eight days. Its vitality was not tested until the twenty-eighth day, on which date it was found to be dead.

The *B. coli,* similarly inoculated into nickel-sulphate broth, apparently grew well. In one day there was definite turbidity, and the colour was somewhat "pinkish." On the sixth day this colour was still present, and by the seventeenth day it had darkened to a "dirty prune-juice" tint. In order to see whether this coloration of the broth was characteristic, the experiment was repeated by inoculating a fresh nickel-sulphate tube. In two days marked turbidity was produced, but no colour, and by the fourth day there was a white deposit. At the end of six weeks, when tested by subculture, the broth was found to be still alive, but in thirteen weeks, when similarly tested, it was dead. The colour production was not repeated. On nickel-sulphate agar the *B. typhosus* did not grow at all, even in six weeks. This was repeated with a similar result, some of the same culture inoculated as a control upon ordinary agar growing well in twenty-four hours.

In the case of *B. coli,* growth upon nickel-sulphate agar was somewhat delayed—no growth being visible on the first day,—and a thick white confluent growth developed by the sixth day in two places only. In four weeks this had not increased, and on testing by subculture was found to be still alive.

Comparing the results obtained with the *B. typhosus* and the *B. coli,* by using nickel-chloride and nickel-sulphate media, one found—

1. That nickel-chloride broth inhibited the growth of, and killed it in eight days, both typhoid and *coli,* whereas nickel-sulphate broth completely inhibited the growth of the *B. typhosus* and killed it in twenty-eight days (and possibly much sooner), while the *B. coli* grew quite well in such a broth, and was still alive after six weeks.

2. That nickel-chloride gelatine and agar inhibited the growth of the *B. typhosus* in a very marked degree, while the *B. coli* was inhibited only very slightly by these media; and—

3. While the *B. typhosus* failed entirely to grow on nickel-sulphate agar, the *B. coli* grew moderately well and was still alive on this medium at the end of four weeks.

Staphylococcus pyogenes aureus.—The next series of experiments was made with the *Staphylococcus pyogenes aureus.* Inoculated into nickel-chloride broth and grown at 37° C., very slight turbidity occurred in twenty-four hours, which increased subsequently, and at the end of one month there was a considerable deposit. On the fifteenth day this broth was found to be still alive, but it was not tested later.

On nickel-chloride gelatine media, typical growth occurred with liquefaction of the gelatine, which was complete in from ten to seventeen days. In some cases the yellow colour of the growth was very well marked.

On nickel-chloride agar, growth was somewhat delayed and did not appear until the fourth day, after which it increased gradually until the fifteenth day and was white in colour. After standing at the room temperature for eighteen months, it was tested by subculture and found to be dead, whereas a streptococcus, cultivated under similar conditions and kept the same length of time, was found to be alive.

When inoculated into nickel-sulphate broth the staphylococcus grew well and produced some turbidity and deposit in twenty-

four hours. By the seventeenth day the deposit was black, possibly a precipitate of nickel sulphide thrown down by the H_2S produced by the staphylococcus during its growth. When tested at the end of fifteen weeks, and again at the end of seventeen and a half weeks, the broth culture was found to be still alive, although the cocci were probably somewhat modified, as a subculture on agar did not begin to grow till the third day. It is possible that the precipitation of the nickel in the form of a sulphide, and so its removal from the culture medium by conversion into the insoluble sulphide, may account for the fact that the cocci were able to live for over four months in this broth.

When inoculated on to nickel-sulphate agar, however, the development of the staphylococcus was inhibited entirely, no growth occurring in any tube on three different occasions.

To summarise the effects of nickel media on the staphylococcus:

1. Nickel-chloride broth only slightly, if at all, inhibited the growth, and the coccus was still alive at the end of fifteen days.
2. Nickel-chloride gelatine and agar media only very slightly delayed the growth of the staphylococcus, and the gelatine was liquefied—although not in the typical funnel-shaped fashion in the stab.
3. Nickel-sulphate broth apparently had no inhibiting effect, and the culture was still alive at the end of four months.
4. Nickel-sulphate agar completely inhibited the growth of the staphylococcus.

Streptococcus pyogenes.—The streptococcus was next tested on these media. A four-day-old growth on agar was inoculated into nickel-chloride broth, and on the third day very slight turbidity was present. The vitality of this broth was tested by subculture on ordinary agar, on the first, third, fifth, seventh, tenth, twelfth, fifteenth, twenty-fifth, and forty-second day, and on each occasion a typical growth of streptococcus on the agar was obtained in twenty-four hours, showing that the streptococcus was able to live for at least six weeks in a nickel-chloride broth. From this nickel broth subcultures on to nickel-chloride agar were made on the fifth, seventh, tenth, twelfth, and fifteenth day, and in each case colonies of streptococcus developed in from one to five days. The only departure from the normal was that the colonies on nickel agar were white and opaque, more

like ordinary diphtheria colonies, and not semi-transparent and bluish in colour, as the streptococcus colonies usually are.

The staphylococcus, similarly inoculated on nickel agar from a nickel broth one day old and four days old, was completely inhibited, and showed no signs of growth. Another very interesting observation was that the subculture made on nickel-chloride agar from the twelve-day-old nickel broth, after standing at the room temperature for eighteen months, was found to be alive, and grew quite typically in twenty-four hours after subculturing on agar. The staphylococcus, under similar conditions, did not show any signs of vitality.

A further point of interest was the following:—The nickel broth when twenty-five days old was inoculated by stab into a nickel-chloride gelatine. On the sixth day no growth was visible, but by the tenth day a few typical colonies were seen, which had not increased on the sixteenth day. At the end of one month many discrete colonies were present and funnel-shaped liquefaction of the gelatine had occurred, and in another week the gelatine was completely liquefied. In order to ascertain whether any contamination had taken place (notwithstanding that the tube was capped with an india-rubber cap the whole time), a subculture on agar was made and a typical growth of streptococcus colonies obtained, and no other organism developed, although the tube was kept for three weeks. The particular strain of streptococcus used had never before, nor has it since, ever shown any tendency to liquefy ordinary gelatine media.

On a nickel gelatine slope inoculated from an ordinary agar culture, by the third day a normal growth was visible, which in one experiment had not increased on the twenty-first day. On that day it was tested by subculture on ordinary agar and found to be alive.

The streptococcus was next grown upon nickel-sulphate agar from a two-day-old culture upon ordinary agar. By the third day growth was apparent, largish white opaque colonies being visible. As was the case when grown on nickel-chloride agar, the colonies were white and opaque, and not semi-transparent as usual. On the sixth day the growth on nickel-sulphate agar was subcultured on to ordinary agar, and the typical small semi-transparent colonies, showing a bluish colour by transmitted

light, were obtained in twenty-four hours. The growth on this agar was then subcultured on to a fresh nickel-sulphate agar, and in two days colonies began to appear. By the eleventh day several whitish opaque colonies were visible, and on the twenty-eighth day these were found to be alive and to give the typical growth when subcultured on agar. At the end of ten weeks, and, in another experiment, at the end of seven weeks, the streptococcus was found to be dead on nickel-sulphate agar. It will be remembered that on nickel-chloride agar it was found alive at the end of eighteen months. An interesting point in connection with the above experiment was that a culture of the anthrax bacillus inoculated on a nickel-sulphate agar tube from the same batch of media, and incubated under the same conditions, failed to grow, whereas the streptococcus, as related above, grew in two days. The effects of nickel media on the growth of the streptococcus may be thus summarised:

1. In nickel-chloride broth the organism seemed to thrive, and was found to be still alive at the end of forty-two days.

2. On nickel-chloride agar the organism grew in from one to five days, the colonies being rather scanty, and white and opaque instead of semi-transparent. In one case extraordinary vitality of the organism on this medium was observed, it being found alive after eighteen months.

3. On nickel-chloride gelatine typical growth was observed, and in one case the medium was completely liquefied at the end of five weeks.

4. On nickel-sulphate agar whitish opaque colonies grew in about two days, and the growth was found to be still alive at the end of four weeks. In one experiment it had died out in seven weeks, and in another in ten weeks, on this medium. The *B. anthracis*, similarly inoculated on nickel-sulphate agar, was completely inhibited.

These experiments are, I think, of considerable interest in demonstrating that the *Streptococcus pyogenes* is not always the frail and feebly resisting micro-organism it is usually held to be. In the case of gangrene of the nose in a child which I brought to the notice of the Society last year, I found the streptococcus associated with the *B. pyocyaneus*. Both organisms grew in a gelatine stab which was inoculated from the excised tissue, the *B. pyocyaneus* causing rapid liquefaction of the gela-

tine, and the streptococcus was found to be alive in this liquefied gelatine at the end of five months. This is another instance of the vitality of a streptococcus.

B. pyocyaneus.—The *B. pyocyaneus* was next tried, mainly with a view to see what effect, if any, would be produced on the formation of colour by the organism. It was inoculated from a one-day-old culture on agar (showing bright green coloration of the medium) into nickel-chloride broth. Very slight turbidity was produced in twenty-four hours, much less than in the control tube of ordinary broth. In forty-eight hours very many actively motile organisms were seen in a hanging-drop preparation from the control tube, whereas in the hanging drop from the nickel broth far fewer organisms were present, and they were much less active than the control, and many bacilli were larger and apparently segmented. On the fourth, sixth, and ninth day the turbidity in the nickel broth was increased, but was much less than in the control. On the nineteenth day the nickel broth was very turbid and much deposit present, but no yellowish-green colour, as in the control tube. At the end of five weeks there was much slate-grey deposit in the nickel tube, but no green colour. On subculturing on ordinary agar the nickel broth was found to be alive on the ninth day.

When inoculated on nickel-chloride agar from nickel broth or from ordinary agar, growth appeared in from one to three days. Frequently this growth was not confluent, but finely dotted, and in no case was any coloration of the medium noticed. So far as tested, the effect on *B. pyocyaneus* of nickel media may be stated as follows:

1. In nickel-chloride broth growth was inhibited to a certain extent, and the organisms were not killed by the ninth day. No colour was produced in the medium.

2. On nickel-chloride agar the organism grew well, and, as before, no coloration of the medium occurred.

B. prodigiosus.—This organism was next tested, mainly because of its chromogenic property. In a nickel-chloride broth of *B. prodigiosus* no sign of growth was apparent in twenty-four hours. A subculture on ordinary agar was made, and growth began on the third day—three colonies only being coloured; the rest were white. On the fourteenth day, and at the end of one

month, four or five colonies were coloured; the rest were uncoloured. Evidently the one day's exposure to nickel broth had modified the colour-producing power of the bacillus.

The original nickel-chloride broth showed no sign of growth until the fourth day, when some turbidity was apparent. By the tenth day a well-marked pink deposit was seen in the control broth, while in the nickel broth the deposit was only slightly pink. At the end of one month the control broth was still a beautiful pink, whereas the nickel broth showed no colour, only slight turbidity.

On nickel-chloride agar a localised growth, which became coloured a deep red by the tenth day, was produced on inoculation from an ordinary agar. When inoculated from an ordinary broth and a nickel-chloride broth one day old, no growth occurred on the nickel agar.

When inoculated from an ordinary agar into a nickel-chloride gelatine shake, no obvious growth, no gas production nor liquefaction of the gelatine occurred.

To summarise, then: nickel-chloride broth and nickel-chloride agar very materially inhibit the growth of the *B. prodigiosus*. In nickel-chloride gelatine shake, it failed to grow at all.

B. anthracis.—When inoculated into nickel-sulphate broth, the anthrax bacillus gave rise to a flocculent deposit in twenty-four hours. The broth was tested for vitality and found to be alive at the end of twelve weeks.

From the same sporing culture on agar which was used for the experiment just described, a nickel-sulphate agar tube was inoculated. No growth occurred on the first day, nor by the end of a month, when the tube was destroyed. This same nickel-sulphate agar, it will be remembered, had allowed the streptococcus to grow.

On the anthrax bacillus, then, nickel-sulphate broth apparently had no harmful effect in twelve weeks, whereas nickel-sulphate agar completely inhibited growth.

Proteus vulgaris.—Nickel-sulphate broth allowed the *Proteus vulgaris* to grow in twenty-four hours, with the production of turbidity and deposit. On the twenty-fourth day the organism on testing was found to be still alive. At the end of ten weeks (and possibly much sooner) it had been killed by the nickel.

On nickel-sulphate agar a very scanty growth was seen in

twenty-four hours, and by the twelfth day it had increased only slightly. On the twenty-third day growth was still scanty, and not confluent as usual, but in the form of single discrete colonies. On the thirty-fourth day it was found to be still alive on subculturing.

Nickel sulphate in broth, therefore, did not inhibit the growth of *Prot. vulgaris* to any extent; the organism was alive on the twenty-fourth day, but dead at the end of ten weeks (possibly earlier). In agar the salt produced considerable inhibition of growth, but the organism was alive at the end of five weeks.

Sarcina lutea.—Inoculated from agar into nickel-chloride broth, slight turbidity was observed in two days. On the fifteenth day there was much turbidity and yellow deposit, and the broth was found to be alive on subculturing.

The experiments made with "copper-sulphate" media were few in number, partly because I had failed in attaining my object with the nickel media, but more especially because I found that the copper sulphate was largely precipitated during the preparation of the media, and I was therefore unable to form any opinion as to the percentage of copper present in the media. Of course it might have been estimated by purely chemical methods, but there was only a minute quantity present, and the organic matter in the medium would have rendered the estimation difficult.

B. typhosus and B. coli communis.—A copper-sulphate broth completely inhibited the growth of these bacilli. On testing for vitality on the thirteenth day both tubes were found to be dead.

On copper-sulphate agar, on the other hand, both organisms grew well, and the relative profuseness of the cultures of typhoid and *coli* was observed. Tested at the end of six weeks, the *B. typhosus* was found to be dead (possibly it was killed much sooner), while the *B. coli* was still alive.

Staphylococcus pyogenes aureus.—In copper-sulphate broth very slight, if any, turbidity was produced in one day, and this did not increase by the fourteenth day. Tested on that day, the broth was found to be dead, and possibly it was dead much sooner.

On copper-sulphate agar growth was quite inhibited, as it was in broth; the material inoculated was dead in six weeks, possibly much earlier.

Streptococcus pyogenes.—In the copper broth this organism fared no better than did the staphylococcus. It showed no signs of growth, and when tested on the fourth day was found to be dead.

On copper-sulphate agar, however, it again showed itself less susceptible to the action of these salts than did the staphylococcus.

Slight signs of growth on copper agar were visible in two days, and on the fourth day typical very fine colonies were present. The colonies remained very minute, even at the end of seven weeks, and when tested at this time were found to be dead.

B. pyocyaneus.—In copper-sulphate broth some turbidity was produced in two days. Tested for vitality on the third day, the broth culture was found to be dead.

On copper agar a good growth occurred in two days; this spread slowly, and at the end of a fortnight covered the surface of the medium. The growth, instead of being confluent, as usual, was finely dotted and almost invisible. No coloration of the medium occurred, and the growth was dead in six weeks (possibly earlier).

B. prodigiosus.—In copper broth very slight, if any, growth occurred, and the broth was dead on the fourth day.

On copper agar it grew well, and was normally coloured in two days. At the end of six weeks there was a profuse growth of a rich dark red colour, almost black in one place. On testing, it was found to be alive, but the subculture on agar did not produce much pigment, even at 22° C.

B. anthracis.—In copper broth growth was inhibited, and the broth found dead on the fourteenth day (possibly it was dead earlier). On copper agar a typical growth occurred on the second day, which increased on the third day. At the end of six weeks the growth was about the same, and on testing was found to be alive.

Proteus vulgaris.—In copper broth no sign of growth occurred in eight weeks. The broth was not tested for vitality.

On copper agar a good growth formed in two days, but rather less than normal. The culture was dead in six weeks, and possibly sooner.

B. subtilis.—A sporing agar culture, ten days old, was inocu-

lated into copper-sulphate broth. In two, three, and four days there was no scum, nor any sign of growth. On subculture the broth was found to be still alive.

At the end of six weeks growth in the broth had still been inhibited, but the spores were not killed, as was proved by sowing a loopful of the copper broth on to ordinary agar, when a typical growth occurred in twenty-four hours.

Inoculation of a sporing culture on to copper-sulphate agar failed to produce any sign of growth, even in six weeks. When the material inoculated was then removed from the copper agar and put on ordinary agar, a typical white, dry, and wrinkled growth occurred in forty-eight hours. Thus the copper sulphate inhibited the development of the spores, but did not kill them, even in six weeks.

The effects of copper may be thus briefly summarised:

1. Copper-sulphate broth probably inhibited the growth of all the organisms tested (*B. typhosus, B. coli, Staphylococcus, Streptococcus, B. pyocyaneus, B. prodigiosus, B. anthracis, Proteus vulgaris,* and *B. subtilis*). They were all killed in fourteen days, and some much earlier, except the *B. subtilis,* the spores of which were found to survive an exposure of at least six weeks to the copper broth.

2. Copper-sulphate agar inhibited the growth of the following organisms completely:—*Staphylococcus pyogenes aureus* and *B. subtilis.*

At the end of six weeks the material inoculated on the copper agar was found dead in the case of *Staphylococcus,* but still alive in the case of *B. subtilis.*

The following organisms grew on copper agar:—*B. typhosus, B. coli, Streptococcus pyogenes, B. pyocyaneus, B. prodigiosus, B. anthracis,* and *B. proteus vulgaris.* Of these, *B. coli, B. prodigiosus,* and *B. anthracis* were found to be still alive at the expiration of six weeks. The remainder (*B. typhosus, Streptococcus, B. pyocyaneus,* and *Proteus vulgaris*) were dead in six weeks, and possibly earlier. *November 4th,* 1902.

7. *On the nature of the yellow colour occurring in cases in which the urine is free from bile pigment.*

By F. H. Thiele.

In a great many diseases there occurs a yellowish coloration of the skin, and sometimes of the conjunctivæ as well, without any trace of bile pigment being at any time present in the urine. The urine in these cases always contains an excess of urobilin, but this excess does not bear any relationship to the depth of the pigmentation observed in the skin. The diseases in which this yellowish pigmentation occurs without any bile pigment being present in the urine are—congested liver from back pressure, as in the nutmeg liver of cardiac disease; cirrhosis of the liver; pernicious anæmia; large internal hæmorrhages, such as are met with in cases of pelvic hæmatocele from ruptured ectopic gestation, certain cases of icterus neonatorum, and in certain diseases such as septicæmia.

The depth of colour observed in the skin varies considerably in these cases. In some there may be simply an earthy pallor, in others a lemon-yellow colour, and in others again a dirty brownish-yellow. The conjunctivæ are not frequently coloured, and usually only in the brownish-yellow cases. In the majority of these cases urobilin is present in such excess as to be detected by direct spectroscopic examination; in others it is less in amount. The depth of colour bears no relation to the amount of urobilin in the urine; thus cases of marked urobilinuria may exist with simply an earthy pallor, and in cases in which the urobilin is much less in quantity the coloration of the skin may be much deeper. Thus in some acute febrile cases, septic cases, and some cases of cardiac disease, there may be a lot of urobilin in the urine and the discoloration of the skin may be only slight; whereas in other cases where there is less urobilin the patient may be deeply tinged, as in one of the cases of pernicious anæmia to be presently quoted. As a rule the cases of cardiac liver, cirrhosis of the liver, and of internal hæmorrhage show more marked discoloration of the skin than the other cases.

All serous effusions in cases of this description are tinged yellow.

The cause of this yellow coloration has been variously ascribed to pigments other than bile pigment. Thus Gubler recognised two varieties of jaundice: the ordinary variety, in which there was bile pigment in the urine, he called l'ictère biliphéïque; the other, in which no bile pigment was present in the urine, he called l'ictère hémaphéïque, the colour of the skin being, according to him, due to a hypothetical pigment—hémaphéïn. This pigment he considered to arise in cases in which the liver cells no longer converted hæmoglobin into bile pigment (owing to toxines), and the colouring matters underwent changes in the blood before excretion in the urine. According to Quincke, this pigment closely conforms with urobilin. Other observers, especially German observers, have attributed this yellow coloration to urobilin. Urobilin, however, has very feeble staining properties, and in alkaline solutions, in which it must exist if it be present in the tissues, it is a much feebler staining reagent still. Other pigments are also not much more powerful than urobilin in this respect. I therefore thought it would be interesting to examine fluids from the bodies of such patients in order to examine the pigments in them. I accordingly applied blisters to the patients and examined the blister fluid; in a few cases I was also able to obtain small quantities of blood during life. Serous effusions were examined when drawn off during life, and after death blood and serous fluids were similarly examined. In all cases uniform results were obtained. The blister fluid obtained in these cases was yellowish in colour, in some cases quite a dark yellow—quite different from the pale, slightly straw-coloured fluid obtained from non-pigmented people.

The pigment obtained from all these fluids gave reactions identical with those of bile pigment. The blister fluid was treated with alcohol and allowed to stand; the albumen was filtered off, and an alcoholic solution of the pigment was obtained. This solution when faintly acidulated yielded no characteristic spectroscopic band, but simply caused slight absorption of the violet end of the spectrum, and in no case was a urobilin band seen at F.

Some of this solution, which was yellow in colour, when gently heated with a few drops of sulphuric acid became green and blue. A few drops of fuming nitric acid carefully added to it

changed it from yellow to green, to blue, to yellow. A watery solution gave, with fuming nitric acid, a typical Gmelin's reaction. Tincture of iodine carefully poured on to the surface of the original fluid gave a greenish-white ring. If some of the original blister fluid be heated with a little sulphuric acid, the albumen coagulates and gets coloured green and blue, and the clear fluid separating is also green.

V. Jacksch's test for bilirubin in the blood-serum was also obtained from the blister fluid. The fluid was poured on to a white porcelain dish and heated to 80° C., when the coagulated albumen became quite green. Blood obtained during life was allowed to coagulate, and the yellow serum left was treated in a similar way with similar results.

Blood removed during the *post-mortem* was centrifugalised; the clear serum was in all cases a deep yellow, and it gave reactions identical with those mentioned above.

Serous effusions were not so deeply coloured as the above-mentioned fluids, but they were all yellowish, and in order of depth were pericardial, pleural, and peritoneal. These were all treated as above, and yielded similar results.

Fluid from effusions in Bright's disease did not give reactions like this, and were very pale straw, almost watery colour. Blood removed at the *post-mortem* from cases other than those mentioned above, after centrifugalisation yielded a pale serum, which did not react in the manner described. Blister fluid obtained from other cases, *e.g.* a case of Addison's disease, was of very pale straw-colour, and did not give the colours mentioned on similar treatment.

Fluids removed from patients in whom there was undoubted jaundice from obstruction were coloured, and reacted like those obtained in the cases under consideration.

Not only was this pigment, which gives reactions identical with those of bilirubin, demonstrable, but, in cases where I was able to obtain sufficient quantities of fluid for examination, Pettenkofer's reaction for bile acids came off after the complete removal of the albumen by alcohol. I was able to demonstrate their presence in cases of cirrhosis of the liver, in cardiac disease with back pressure, and in one case of pernicious anæmia.

Further, in several cases in which *post-mortem* examinations were made there was seen to be bile staining of the hepatic

lobules, visible both micro- and macroscopically. This was seen in cardiac livers, cirrhotic livers, and in the liver of one fatal case of pernicious anæmia.

These facts seem to prove that the pigment which colours the skin in these cases is bilirubin or bilirubin slightly modified, and that in some cases, at all events, there is a real obstructive jaundice.

In cirrhotic and cardiac livers the jaundice may be explained on mechanical grounds.

In pernicious anæmia it may be that the toxines spoken of by Dr. Hunter as causing the hæmolysis in the portal system may act as irritants to the bile canaliculi during their excretion by the latter, and so cause swelling and catarrh, and thus produce interference with the biliary flow, which with the co-existing polychromia sets up the slight jaundice.

In septic diseases, accompanied by jaundice of this description, the cause may be a similar irritation and catarrh of the biliary canaliculi by the toxines formed in the body and excreted by them.

In icterus neonatorum the cause is also probably mechanical.

With regard to the yellowish coloration of the skin seen in cases of large internal hæmorrhage, as in pelvic hæmatoma, the problem is very interesting. The blister fluids obtained from such cases gave results identical with those mentioned above. I was never able to obtain enough fluid to be able to test for bile acids.

In one case examined the patient was a man with a large hæmatoma of the back. The patient became yellow about a week after the injury, and the urine contained a large quantity of urobilin. The blister fluid of the patient reacted in the way mentioned above. The hæmatoma was aspirated, and from the fluid removed I extracted with alcohol, after centrifugalisation, from the resulting dark yellow serum, a yellow pigment, hæmatoidin, giving all the reactions of bile pigment. It was not so stable as bile pigment, for after some time it lost its characteristic reaction. It may therefore be possible that hæmatoidin is taken up from these extravasations, and is the cause of the jaundice. But against this is the fact that the appearance of the jaundice is so rapid that it seems improbable that hæmatoidin is formed as quickly as would be necessary if it were the

cause of the pigmentation. In the case quoted above the hæmatoma was aspirated three weeks after the onset. Then, again, in other cases the jaundice may appear more rapidly still; thus it has been noticed that two days after the slipping of an abdominal ligature the patient became very yellow and had a large amount of urobilin in the urine. Again, the depth of the jaundice bears no relation to the amount of the hæmorrhage as determined in cases of pelvic hæmatocele. Thus with a large hæmorrhage there has been no apparent coloration, and in a small one marked yellowness has occurred. It may be, therefore, that in these cases it is a true jaundice, and that with the absorption of colouring matter from the extravasation, which must occur to give rise to the urobilinuria, some substance, which is irritating to the bile-ducts, and formed in the extravasation, may be absorbed.

From these results it seems clear that, except for the last group of cases, the colour is really due to bile pigment, and that the so-called "urobilin" jaundice is a true jaundice.

It may be that the pigment may be converted by the kidney into urobilin before excretion, but one would expect in such a case to have urobilinuria to a certain extent running parallel to the jaundice, which, however, is not the case; but this supposition is not necessary, since it can be explained that bile will only appear in the urine when it has reached some definite quantity in the blood, since cases occur with the pigmentation and only urobilinuria at first, but which subsequently get bilirubin appearing in the urine.

The following is an analysis of the cases examined:

Pernicious anæmia.—Three cases.

One case was fatal. Pigmentation was very marked; conjunctivæ yellow. Urine had only slight excess of urobilin. The fluids were very yellow. The liver *post mortem* showed bile staining.

The other two cases were lemon-yellow; the blister fluid was deep yellow. Conjunctivæ were normal. Slight excess of urobilin present in the urine.

In all three cases the blood analyses showed typical changes.

Icterus neonatorum.—Two fatal cases.

In neither was bilirubin or urobilin present in the urine. The

conjunctivæ were tinged. After death the serous fluids all yielded above-mentioned results.

Pelvic hæmatocele.—In one case was the blister fluid examined. Patient quite yellowish brown; conjunctivæ yellow. Urine had a large excess of urobilin. Blister fluid was yellow, and reacted in the way before stated. Several other cases were noted with regard to the depth of colour and amount of hæmorrhage, and the time of onset of the colour. Thus—

1. Ruptured ectopic gestation. Large hæmatocele; no jaundice at all; urobilin in the urine.

2. Ditto. Small hæmatocele; jaundice noted on the third day after the symptoms of rupture; eyes yellowish; urobilin in urine.

3 and 4. Ditto. Small hæmatoceles; no trace of jaundice whatever; very slight excess of urobilin in the urine.

5. Giving way of ligature in the omentum after operation. Jaundice appeared within forty-eight hours of the operation; large hæmorrhage; jaundice was very marked; large quantity of urobilin in the urine.

Hæmatoma.—Man with fractured ribs. Skin was yellow; eyes tinged. Urobilin was in excess in the urine. The blister fluid was yellow, and reacted in the usual way. The hæmatoma contained large quantities of hæmatoidin.

Cardiac disease with urobilinuria.—Over twenty cases were observed. In these the colour varied considerably from an earthy pallor to brownish yellow. In all cases the blister fluid was yellow, and gave the usual results. In some cases the conjunctivæ were coloured as well. In these cases also serous effusions removed before and after death, and blood removed at the *post-mortem* gave the reactions.

In one case the patient was brownish yellow, with yellow conjunctivæ, and had no bilirubin in the urine till the day before death, when it was detected for the first time.

Cirrhosis of the liver.—Ten cases.

These all yielded the same results. In one of these also the patient subsequently developed bilirubin in the urine.

Septicæmia.—Two cases.

In both these was a yellow tinge in the skin, but none in the conjunctivæ. In one the blister serum was examined with the above-mentioned results. In the other case the patient was

blistered severely before admission, and the edges of the blister wound were quite green. The patient had marked excess of urobilin.

These experiments also confirm von Jacksch's results as regards the presence of bilirubin in the tissues in cases of urobilinuria.

My best thanks are due to the members of the staff of University College Hospital for their kindness in allowing me to make use of their cases for the purposes of this investigation.

November 18th, 1902.

6. *The inhibitory effect on bacterial growth of the viscid exudate in tabetic joints, etc.*

By C. G. Seligmann.

During a series of attempts to cultivate micro-organisms from a number of joints in which chronic degenerative changes, accompanied by more or less exudation, had taken place, the fluid from two examples of Charcot's joint occurring in typical cases of locomotor ataxy was examined. In both these cases the fluid was strongly alkaline, orange-yellow in colour, and highly viscid. In the first case about 18 oz. were withdrawn from the left knee in two tappings; from the second case rather less than 4 drachms were obtained. The fluid from both patients was sterile, and, indeed, proved to have a remarkable power of inhibiting the growth of bacteria. A small quantity of fluid from the first case was accidentally exposed for days in the laboratory in an evaporating basin; it did not decompose, but slowly dried into a firm, brittle, yellowish-brown film at the bottom of the vessel. Absence of decomposition was also observed when pieces of fresh blood-clot were mixed with about an equal amount of fluid and similarly exposed, though here there was later a vigorous growth of moulds on the almost dry surface of the mixture of clot and fluid.

About this time I was informed by Drs. T. B. Hyslop and W. S. Colman that they had clinically noted facts which seemed to show that the fluid in a Charcot's joint does not

easily decompose. The former instanced a case of a patient lately in Bedlam Asylum, in whom for nine months there had been a chronic discharge from a Charcot's knee, which, in spite of extreme carelessness on the patient's part, had not led to suppuration within the joint. Dr. Colman's experience was in the case of a male tabetic aged 40, with a large effusion into the shoulder-joint. This was opened and drained. The fluid escaped constantly, and, although all attempts at antiseptics were soon given up, the discharge remained sweet. At the time of operation some of the fluid was collected in an ordinary stoppered bottle. This was overlooked, but at the end of a fortnight the fluid still remained clear. The stopper was then removed, and since, at the end of a further fortnight, the fluid was clear and without smell, some putrid matter was added, without, however, provoking putrefaction. These observations, which suggested that the exudate in tabetic joints had the power of killing bacteria, or at least of inhibiting their growth, led me to make a series of experiments *in vitro*, in which active growths of micro-organisms were submitted for varying lengths of time to the action of the fluid.

Loops of vigorous broth cultures, of freshly isolated strains of *Streptococcus pyogenes*, *Staphylococcus aureus*, and *S. albus*, and laboratory races of *B. coli* and *typhosus* were inoculated into small portions of the fluid, which were then incubated at the body temperature for a fortnight. At no time during this period was there any evidence of growth in the tubes; the fluid remained clear, and of the same yellow colour and viscid character as before inoculation. On examining films a few scattered organisms were seen; these were considered to be, and doubtless were, the individuals actually carried over. All the species of organisms mentioned, however, remained alive in the fluid, and when loops of the latter were, at the end of a fortnight, carried over into broth tubes, normal vigorous growths were in every case obtained. This is a somewhat surprising result in the case of *S. pyogenes*, which, without constant passage, is notoriously difficult to keep alive *in vitro*. The above experiments refer to the fluid withdrawn from the knee-joint of the first case. Identical results were obtained with the fluid removed from that of the second case, *S. citreus* and *B. coli* and *typhosus* being the organisms experimented with.

Loops of the fluid with these organisms in suspension, when carried on to broth, still gave normal growths thirty-six days after the organisms were added to the fluid. The growth of *S. citreus*, however, seemed somewhat weakly. Thus in both cases the fluid possessed no bactericidal power, but showed a strong inhibitory effect on bacterial growth.

By means of hanging drops, the effect of the fluid from the second case on *B. coli* and *typhosus* was further studied. It was found that *B. typhosus*, from a young, actively mobile broth culture, was completely immobilised in twenty minutes, and that the individual bacteria had aggregated into clumps, for the most part smaller, but no less dense than occurs in a positive Widal reaction. Even in a dilution of one part of knee fluid to three of broth, there was loss of motility, and a few loose clumps formed in thirty minutes. With a dilution of 1 in 5 no effect on the bacilli was noted. *B. coli* behaved in much the same way; in a dilution of 1 in 3 almost all the bacteria of a moderately mobile culture became immobile, with the formation of some loose clumps in ten minutes. With a dilution of 1 in 5 no clumping was observed, but the organisms had completely lost their motility in thirty minutes. The blood-serum from this case in a dilution of 1 in 2 never in the least degree immobilised or agglutinated *B. typhosus* or *coli*.

For comparison, a few drops of apparently normal synovial fluid, which itself putrefied rapidly, were removed from the knee-joint of a leg immediately after amputation through mid-thigh for senile gangrene of the foot; this fluid quickly immobilised and clumped *B. typhosus* and *B. coli* in a dilution of 1 in 2, but since this individual's blood clumped both these organisms in a more marked degree, this result is hardly comparable with that given above. With the various staphylococci nothing resembling agglutination was ever seen.

As already stated, the fluid from both cases showed no sign of growth when incubated at 37° C. after inoculation with various organisms. If, however, an equal quantity of broth were added to the fluid, an abundant growth occurred, and if such a mixture were left exposed, putrefaction rapidly took place.

As to the cause of the inhibitory effect exercised on bacterial growth by the fluid, two hypotheses are possible.

This result might be due (1) to the chemical action of some

constituent of the fluid, or (2) to its physical condition. That it is not due to the former is, I think, suggested by the complete abolition of the inhibitory effect of the fluid by dilution with a small quantity of broth.

The result of the chemical examination of the fluid removed from the first case, conducted by Dr. J. B. Leathes, to whom my best thanks are due, shows that the absence of growth could not be due to lack of material capable of supporting bacterial life. This point was further proved for the fluid from the second case by diluting it with about twice its volume of normal saline, when putrefaction rapidly occurred.

Acetic acid gives a dense coherent precipitate, which redissolves unless the acid is added in sufficient quantity to cause a decidedly acid reaction. In a larger excess of the acid this precipitate dissolves entirely. The filtrate from this precipitate is no longer viscid and glairy, but gives a precipitate on saturation with sodium chloride, or on dilution with several volumes of water. Whether this precipitate be filtered off or not, the filtrate from the acetic acid precipitate gives an abundant coagulum on boiling. The filtrate from this coagulum gives no biuret or other proteid reaction, but with copper and alkali a greyish-blue precipitate, which retains its colour on boiling, is produced.

The substance precipitated by acetic acid shrinks to a tenacious, sticky, coherent mass of a bright orange-yellow colour. It could be dissolved in 1 per cent. sodium carbonate, and this solution after filtration was reprecipitated several times with acetic acid. After the first precipitation, acetic acid caused a precipitate that with each precipitation tended to become more and more flocculent and less coherent and sticky.

A portion of this product, which gives the Millon, Biuret, and Xanthoproteic reactions, was, on incineration, found to contain no P_2O_5, though the original joint fluid when dried and incinerated contained this substance in considerable amount. On hydrolysis, by boiling with weak hydrochloric acid for half an hour or more, a small amount of some substance that reduces Fehling's solution was obtained.

A small quantity of a non-proteid substance containing iron was precipitated by copper from the filtrate from the acetic acid precipitate after removal of the proteids by coagulation.

Thus the fluid contains—

1. A substance precipitated by acetic acid to which its glairy consistency is due, which is not mucin, but is a glyco-proteid or mucoid.

2. A globulin.

3. An albumen.

No other proteid is present.

A point of considerable interest is raised by the presence of a large quantity of a "mucoid" substance in solution to which the viscid character of the fluid was almost certainly due, and which is probably responsible for its inhibitory action on micro-organisms. Arloing* has experimented with the mucinous secretion of the red slug, for a filtered solution of which he proposes the term mucidine. This fluid, though not itself sterile, possesses a marked effect on bacteria. Mucidine sterilised by passing through a porcelain filter was mixed with broth in varying proportions, so that solutions containing respectively 33 per cent., 50 per cent., and 66 per cent. of mucidine were obtained. These were inoculated with several loops of vigorous broth cultures of *B. diphtheriæ, typhosus, anthracis,* and *tuberculosis.* After six days the 50 per cent. mucidine solution was sterile in each case, and the 33 per cent. mucidine solution had exercised some inhibitory influence. A smaller proportion than this of mucidine exercised no inhibitory effect. Arloing does not mention how viscid his mucidine was, but as it slowly passed through filter-paper its viscidity cannot have been extreme.

The results of Arloing's experiments with mucidine differ from my own with tabetic joint fluid, in that the latter does not, even when allowed to act for weeks, kill organisms immersed in it. The loss of their inhibitory effect on dilution is, however, common to both substances, and this effect can be observed with other viscid exudates.

Owing to the kindness of Mr. G. H. Makins I have had the opportunity of examining a small quantity of a highly viscid fluid removed by him under aseptic conditions from the right knee-joint of a woman, aged about 25, who had for about a year com-

* F. Arloing, 'Journ. de Phys. et de Path. générale,' Paris, tome iv, No. 2, 1902. In the 'Lyon Médicale' for Jan. 19th, 1902, Arloing describes experiments with "mucidine" on *B. diphtheriæ,* which in a 50 per cent. solution in broth did not prevent a slow growth of the bacillus.

plained of stiffness, pain, and swelling in the joint. Her trouble was at first associated with a vaginal discharge, probably gonorrhœal in origin, although gonococci or organisms of any kind could not be detected in the knee fluid, of which there was too small a quantity for detailed chemical examination. That it resembled the fluid from the tabetic joints in containing a mucoid substance, but no true mucin, was, however, shown by acetic acid causing a precipitate soluble in excess of the acid. When the fluid was first withdrawn from the joint there floated in it a quantity of fibrinous flakes and shreds. These subsequently settled at the bottom of the vessel, leaving a clear, pale straw-coloured viscid fluid, which, although not sterile, did not putrefy on exposure to air. The effect of this on various bacteria was tested in hanging drops. One loop of a young, vigorous culture of the organism was added to four loops of the knee fluid, and the whole incubated for four days, the hanging drops being examined at the end of the first and fourth day. In every case a control hanging drop of the broth culture of the organism used was put up and treated in the same way. All these controls grew vigorously. With *S. citreus*, *B. anthracis* and *typhosus* no growth resulted in the mixed drops, the *typhosus* being immobilised. *S. aureus* possibly grew slightly, but certainly very much less than in the control. *B. coli* did not grow, became immobile, and formed small, loose clumps. As this fluid was not sterile, a very mixed growth was obtained on transferring loops from the incubated hanging drops to broth, but it was clear in the case of *B. anthracis* and *S. citreus* that these organisms had been in no way harmed by four days' immersion in the fluid.

What appears to be an example of the same effect was seen on exposing to the air of room temperature the sticky fluid of varying degrees of viscidity removed from ovarian cysts. Moderately viscid examples putrefied slowly, becoming more fluid as they did so, and at first seeming to resist putrefaction to a marked degree; if such a fluid were diluted with sterile water or saline, putrefaction took place rapidly, and the same held good on dilution in the case of one viscid fluid (sp. gr. 1012), which remained sweet when exposed for ten days in an undiluted condition. On microscopical examination of the undiluted fluid at the end of the time mentioned only occasional organisms were to be seen,

and these never appeared in groups or filaments, as would probably, to some extent, have been the case had such organisms been in favourable conditions for multiplication. Perhaps, however, the most convincing experiment bearing out the point of view taken—namely, that it is the physical condition of viscid fluids which inhibits bacterial growth—is the following:

If capped tubes of broth and jelly containing the same quantity of medium of the same reaction be left for twelve hours in an incubator at 37° C., and both tubes be inoculated with equal amounts of a broth culture of *B. coli* or *typhosus*, and again incubated for from twelve to twenty-four hours, the growth in the viscid jelly will at no stage be seen to be as advanced as that in the non-viscid broth. If plates be poured from two such cultures, precautions being taken to use plates of the same area, and culture tubes containing the same amount of medium, the difference in the number of colonies which develop is very marked. *January 20th*, 1903.

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7. *Observations on the resistance of* Staphylococcus pyogenes aureus *to perchloride of mercury.*

By F. W. Andrewes.

It is a well-recognised fact that *Staphylococcus pyogenes aureus* is one of the most resistant non-sporing organisms. Its exceptional resistance extends to heat as well as to chemical disinfectants, so that it is commonly chosen as a test organism in experiments on disinfection. Sternberg gives its thermal death point as 58° C. with ten minutes' exposure, but this is sometimes too low. In a recent experiment, in which I contrasted *Staphylococcus aureus* with *B. coli communis* under identical conditions, viz. heating to 60° C. side by side, the staphylococcus survived sixteen minutes' exposure, though the colon bacillus lived only six minutes. It cannot be doubted that different strains of staphylococci vary somewhat in their resistance, both against heat and against chemicals. But there is a group of chemical substances, viz. the persalts of mercury,

against which *Staphylococcus pyogenes aureus* exhibits a resistance out of all proportion to that which it shows against disinfectants of the phenol group. In its action upon most non-sporing bacteria one is accustomed to regard a 5 per cent. solution of phenol as somewhere equivalent to a 0·1 per cent. solution of mercuric chloride. Both solutions ought to kill in a very short time, a minute or two at the outside. Yet in the case of *Staphylococcus aureus* the relation between the two solutions does not hold good. Carbolic acid will kill it almost as easily as it will kill colon bacilli, but the persalts of mercury will not. Mercuric chloride, in 0·1 per cent. solution, kills most non-sporing bacteria very quickly, but it takes a disproportionately long time to kill *Staphylococcus aureus.* Everyone who has used the coccus in disinfection experiments with the salts of mercury must have been struck by these facts, but it is quite time that much more emphasis should be laid upon them than is usually the case in text-books. For the mercuric salts are very widely relied upon in practical disinfection, and *Staphylococcus pyogenes aureus* happens to be one of the organisms against which routine surgical disinfection is specially aimed.

In some recent observations which I have made on the subject, I have obtained some facts and figures which came to me as a great surprise. They are possibly quite exceptional; the strain of *Staphylococcus aureus* with which I worked was evidently one of unusual resistance. But routine disinfection must be prepared to meet the exceptional as well as the commonplace, so that the mere fact that staphylococci can, even if seldom, possess the resistance about to be described, is a fact seriously to be reckoned with. Another practical point deserves to be emphasised. It is well recognised that perchloride of mercury varies immensely in its disinfectant power according to the medium in which it acts. Laboratory experiments conducted in distilled water are no real test of its practical value in clinical use. It is shown that the presence of other soluble chlorides, such as sodium chloride, interferes with its germicidal powers, and on the modern theory of solutions this is explained by the diminution in the number of free mercury ions. It is also known to everyone that the presence of albuminous matters interferes with the germicidal powers of mercuric salts, owing to the formation of a relatively inert

combination of the mercury with the proteid. The experiments which I have to describe were carried out in distilled water, in physiological salt solution, and in ordinary nutrient peptone broth. The results were, of course, widely different in the different media. I did not use serum, but the results obtained in peptone broth were at once the most surprising and also the most practically important, since peptone broth approximates more closely to the animal fluids requiring disinfection than mere salt solution or plain water.

The strain of staphylococcus employed was a casual one which happened to be at hand in the laboratory. I could not trace its exact origin, but it had been recently cultivated from some abscess or skin eruption. It formed a rich orange pigment, and was in all respects typical. Its resistance was first tested in broth culture. Five c.c. of a forty-eight-hour old broth culture, and 5 c.c. of a 0·4 per cent. solution of mercuric chloride (which I personally weighed out and made up) were mixed together, giving a total strength of 1 in 500. Subcultures were made at intervals by transferring two platinum loopsful to sterile broth tubes. Good growth occurred in all cultures taken up to forty-five minutes, which was the limit of the experiment. Mr. Gordon Watson, who was working with me, controlled a number of the experiments, doing them independently in duplicate. In this case he got growth after forty minutes, but not after forty-two and a half minutes. We always controlled our results by making agar-agar subcultures from the broth tubes which yielded growth, in order to be sure that the growth which occurred was truly *Staphylococcus aureus* and not a chance contamination.

The same strength of the disinfectant was tested, acting in pure distilled water, by making a turbid emulsion from an agar-agar culture, free from visible lumps, and mixing it with an equal measured volume of the 0·4 per cent. mercuric chloride solution. I got growth after twelve and a half minutes, and Gordon Watson growth after ten minutes. This same mercuric chloride solution in a strength of 1 in 500 killed *B. coli communis*, both in watery solution and in broth culture, in less than fifty seconds.

It now occurred to me that it might be possible to produce, from so resistant a strain of the cocci, an increasingly resistant

strain, by using in each succeeding experiment the culture which had last survived in the preceding experiment, and which might be presumed to represent the progeny of the cocci most resistant against the disinfectant employed. There is no need to detail all the intervening experiments. They were carried out with great care, and, distrusting the mercuric chloride solution which I had myself made up, I had a fresh solution prepared with extreme accuracy by the chief dispenser at St. Bartholomew's Hospital. The final results, after the resistance of the strain had been thus apparently increased by a number of passages through mercuric chloride, were as follows:

In pure redistilled water, the cocci resisted a strength of 1 in 500 mercuric chloride for twenty minutes, but not for twenty-five minutes.

In pure redistilled water they resisted a strength of 1 in 1000 of the perchloride for fifty minutes, but not for sixty minutes.

In a solution of sodium chloride (0·3 per cent.) they resisted 1 in 1000 perchloride for eighty minutes, but not for ninety minutes.

An emulsion in nutrient peptone broth containing a total strength of 1 in 1000 of perchloride, was alive at the end of four hours. Every subculture up to four hours grew vigorously; how much longer it remained alive was not determined.

This high degree of resistance against mercuric chloride was equally apparent against the biniodide. Mr. Gordon Watson got a good growth from an emulsion of the cocci in a 1 in 500 biniodide of mercury solution (made up in water with potassium iodide) after thirty minutes. But it did not extend in the least to disinfectants of the phenol group. I found that the cocci were killed by 1 in 40 carbolic acid in less than two minutes (probably much less), and by a 1 in 400 solution of medical izal in less than one minute. I tested the restraining power of carbolic acid upon it. It grew well in broth containing 0·2 per cent. phenol, and feebly in 0·28 per cent. One third per cent. phenol inhibited growth, but did not kill in forty-eight hours. One half per cent. phenol killed in forty-eight hours.

The above experiments indicate that *Staphylococcus pyogenes aureus* has, against the persalts of mercury, a resistance which may almost be described as specific. The fact may be familiar enough to many practical bacteriologists, but it certainly does

not receive the attention it deserves in text-books on the subject. Of six standard works on bacteriology, I found only in one or two casual references to the matter, and this may serve as an excuse for my bringing it forward this evening. It has been suggested that the phenomenon depends upon the glutinous material secreted by the staphylococci, and binding them together in zoöglœa form. This may form an inert compound with mercuric salts which protects the cocci themselves from their action. *January 20th,* 1903.

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8. *An epidemic disease characterised by nodular lesions, occurring amongst laboratory guinea-pigs.*

By Leslie Milburn.

(From the Bacteriological Department, Middlesex Hospital.)

During the summer months of 1901, two or three guinea-pigs, which had been inoculated for different diagnostic purposes at the Middlesex Hospital, and some animals which had not been under experiment at all, died, each of them showing a tubercular or nodular condition of various internal organs, at first sight suggestive of a tuberculosis caused by Koch's bacillus. Isolated cases showing a similar condition occurred at intervals during the following autumn, and during the winter the outbreak assumed epidemic form. The disease spread chiefly among guinea-pigs, but one or two rabbits died showing similar lesions.

The origin of the outbreak could not be ascertained, but it soon became evident that the disease was being spread among the animals, probably by infection through the alimentary canal.

In none of these cases could *Bacillus tuberculosis* be found in cover-glass preparations made from the softened lymphatic glands.

The *post-mortem* appearances most commonly presented by the guinea-pigs were—

A marked enlargement, with caseation and softening, of the mesenteric glands; great enlargement of the spleen, this organ being studded throughout with nodules, varying in size from that of a pin's head to that of a hemp-seed.

The liver is enlarged, and nodules similar in appearance to those in spleen are scattered throughout the organ. As a rule the nodules in the liver are smaller and in a less advanced stage of caseation than those seen in the spleen.

The lungs frequently show no obvious change; at other times they show either areas of local congestion or patches of solidification, appearing to the naked eye as greyish, slightly raised islets, surrounded by a zone of congestion.

Infection of the kidneys was not observed in guinea-pigs. The condition seen in the rabbit differed somewhat from that seen in guinea-pigs.

In the rabbit the condition was evidently more chronic; the mesenteric glands were greatly enlarged, although but little softening had occurred.

The intestines were bound down around the enlarged glands by numerous firm organised adhesions. The spleen showed numerous discrete nodules, the caseous portions of which easily shelled out from a surrounding well-marked capsule. The kidneys also showed two or three nodules.

From these cases an organism showing the following characteristics was isolated:

Morphology.

In hanging-drop preparations from a broth culture twenty-four hours old the organism is seen to be a short bacillus with rounded ends; either extremity is slightly broader than an intervening clearer zone, which appears somewhat constricted. This central clear zone is sometimes so marked as to give the bacillus the appearance of a diplococcus.

The bacillus is seen single, in pairs end to end, and in short chains; sometimes two or three chains are seen lying together, giving the appearance of skeins of bacilli.

Brownian movement is shown by the isolated bacilli; otherwise the bacilli are immotile.

In stained film preparations from solid media the bacillus frequently presents well-marked bipolar staining. The length

of the bacillus varies considerably. Some quite short, oval forms are seen, and coccal forms are not uncommon. The shorter forms of the organism stain evenly.

The bacillus is decolourised by Gram's method.

Cultures.

Broth.—After twenty-four hours' growth the broth is slightly turbid, showing also a fairly marked floccular deposit at the bottom of the tube. At the end of three days a delicate film forms on the surface, with a certain amount of turbidity of the broth for the upper third of the medium; at the bottom of the tube is a well-marked deposit, general turbidity extending upwards over the lower third of medium, while the intervening middle third of broth remains more or less clear. When seen in this condition a broth culture presents a very characteristic appearance, but this appearance is destroyed by the slightest shake.

Gelatine streak.—Growth occurs at 22° C., giving rise to a greyish, semi-transparent streak, which becomes yellowish and more opaque with age. The gelatine is not liquefied.

Gelatine stab.—Growth occurs along the stab with slight spreading out on the surface.

Gelatine shake.—A general turbidity of the medium occurs without any formation of gas.

Agar.—At blood temperature growth takes place along the track of needle, forming a broad greyish streak.

Glycerine agar.—On agar, with 1 per cent. glycerine added, growth occurs, but to a much less extent than on plain agar.

Maltose agar.—A very free greyish growth occurs, which becomes slightly yellowish after two or three days. Growth is more abundant on this medium than on any other tried.

Glucose agar stab.—Growth takes place along the stab without any fermentation of the sugar.

Milk.—Growth takes place without any obvious change in the medium.

Potato.—No apparent growth takes place within five days.

Litmus broth.—Growth occurs in both red and blue tubes without any obvious change in the reaction of the medium.

Indol reaction.—The indol reaction is given in broth cultures after three or four days' incubation.

Inoculation and feeding experiments.

These experiments were kindly performed for me by Mr. A. G. R. Foulerton.

Guinea-pigs.—0·5 c.c. doses of twenty-four-hours-old broth cultures were injected both intra-peritoneally and subcutaneously. The guinea-pigs which had received the intra-peritoneal injection died in from four to five days, showing at the *post-mortem* an excess of slightly turbid fluid in the peritoneum, and deposit of fibrin especially marked around the spleen, pancreas, and between the lobes of the liver. No nodules were found in any organ. The subcutaneous inoculations killed in from five to ten days. The lesions found *post mortem* varied with the time the animal had survived after inoculation. When death occurs early the spleen is enlarged, and appears coarsely granular; the liver is congested; the site of inoculation swollen and caseous; the lymphatic glands leading from the site of inoculation are enlarged.

In later cases the nodular and caseating condition becomes more apparent. At the site of inoculation is a large swelling, which on section is seen to be caseous and softened. The femoral, inguinal, and lumbar glands are enlarged and caseous, the first of these being softened, and containing creamy pus.

The spleen is found enlarged, and the whole organ packed with small caseous nodules. The liver is enlarged, congested, and shows numerous grey points scattered throughout its substance. One or two grey points, surrounded by an area of congestion, were found in the lungs. A bacillus similar to that inoculated was obtained in pure culture from a nodule in the spleen.

A twenty-four-hours-old broth culture was sprinkled over the food of four guinea-pigs.

The first pig died on the ninth day. *Post mortem* the intestines were found studded throughout their course with small, yellowish nodules; neither spleen nor liver showed signs of infection.

Two other pigs died on the eleventh day, showing a condition similar to that found in the first pig. On the fourteenth day

the fourth pig was killed; *post-mortem* condition appeared similar to the other three. There were also a few small greyish nodules in the liver.

White mice.—Intra-peritoneal inoculation of 0·25 c.c. killed in from two to three days. The *post-mortems* showed peritonitis, considerable enlargement of the spleen, and in one case a collection of fluid in the pleuræ.

Linnets.—0·5 c.c. injected into pectoral muscle killed within two to four days. The muscle at site of inoculation was found to be swollen, and of a pale drab colour. No obvious lesions could be found in any of the viscera.

Four linnets, whose drinking-water was inoculated with the bacillus, died, three on the third day, the fourth on the seventh day.

Post-mortems on these birds showed little of note. The intestines appeared slightly paler than normal, and in one case the liver had a mottled appearance.

Histology.—Microscopic examination of stained sections from the infected tissues showed the caseous nodules to be composed of accumulations of small round-cells, the more central zones of which were necrotic and stained badly. In the centre of these patches clumps of the characteristic bacilli were seen.

In the case of sections from the linnet's muscle the appearances differed from this. Here the bird had evidently died before sufficient time had elapsed for the production of the typical caseous nodules. The muscle-fibres themselves were feebly stained, and in places forced apart by the invasion of large masses of the bacilli. The veins in these sections were seen widely dilated and filled with blood; a few small round cells were seen surrounding the vessels.

The occurrence of a nodule-producing disease of this description occurring amongst guinea-pigs is of great interest in view of the possibility of its confusion with tuberculosis, unless *Bacillus tuberculosis* is always found in smears from organs before diagnosis is given.

Should the animal die in the early stages of the disease, the points of similarity between the two are many, but in the more advanced condition, or if the time of infection were known, there could be no confusion; the much more rapid progress of

the disease just described, the early softening of infected glands, the great enlargement of the spleen, packed with large caseating nodules, and frequently surrounded by a fibrinous exudate, produces a picture easily distinguished from tuberculosis.

Bacilli from cases of so-called pseudo-tuberculosis have been isolated by several other observers. Muir isolated from cage-birds an organism very similar to the one just described. He considers his bacillus to be identical with those isolated by Nocard, Pfeiffer, Malassey, etc., classed under the term "pseudo-tuberculose zoogléïque." Klein has also obtained a similar bacillus from milk.

The only points of difference between Muir's bacillus and that isolated from the cases here described, are that Muir's bacillus grows equally well on glycerinated or non-glycerinated agar, whereas my cultures have always shown much less growth on glycerinated media. Muir also was unable to infect guinea-pigs by feeding, while all my guinea-pigs so treated were easily infected. Charrin and Roger met with a similar nodular disease occurring spontaneously in guinea-pigs. This bacillus was quite inhibited by glycerine added to the media, and developed easily on potato.

Courmont isolated a bacillus from a nodular condition of the pleuræ of a cow. His bacillus gave a coffee-coloured growth on potato, and is easily distinguished by showing free motility,

"Les descriptions des différents auteurs concordent mal, peut-être se rapportent-elles à un certain nombre de variétés d'une même micro-organisme." (Besson.)

May 6th, 1902.

9. *A case of tuberculosis of the œsophagus.*

By F. C. Shrubsall and W. T. Mullings.

Our excuse for bringing forward this case is the comparative rarity of this pathological condition, no case of the kind, so far as we can ascertain, having been yet recorded in the British Isles.

The specimen shown is from a man aged 54, who was admitted to the Brompton Hospital under the care of Dr. Acland (to whom we are indebted for permission to show the specimen) on March 25th, 1902, suffering from a left-sided pneumothorax, and who died on May 17th of the same year.

Family history.—This was unsatisfactory, the patient's father and one sister having died from pulmonary tuberculosis and his mother from tuberculous enteritis, while there had been cases of tuberculosis in the preceding generation.

Personal history.—The patient was an upholsterer by trade, and in the course of his occupation inhaled considerable quantities of dust. To this he attributed the fact that he had become a fairly free drinker. During the past six years he had enjoyed fairly good health, except that he had suffered from a slight amount of "winter cough." His present illness commenced at Christmas, 1901, with cough and expectoration, which had gradually increased, so that on admission he was bringing up about a pint of frothy expectoration daily; at times this had been streaked with blood. The patient's breath had gradually been getting shorter, and on admission to the hospital his dyspnœa was considerable, even when lying quietly in bed. The commencement of the dyspnœa had not been sudden, nor had there been any other symptom to indicate the onset of the pneumothorax. During the three months prior to his admission he stated that he had lost much flesh, but he had never at any time experienced any pain or difficulty in swallowing.

Physical signs.—On admission there was evidence of the presence of a hydropneumothorax on the left side, the heart being displaced far to the right, together with extensive tuberculous disease, involving all the lobes of the right lung. The temperature was of the intermittent type, rising to about 100° F. every evening. A laryngeal examination on May 5th (twelve

days before death) revealed slight swelling of epiglottis and aryepiglottic folds, but no other signs of disease of the larynx, while throughout his stay in hospital there were no signs of lesions of the tonsils, pharynx, or back of the tongue. His liver could be distinctly felt two inches below the costal margin, and his spleen was palpable. There were no evidences of disease in other organs. His urine was normal throughout.

On April 9th his left pleural cavity was aspirated (three pints of serous fluid being evacuated), and then washed out with boric acid solution, a procedure followed by slight relief to his dyspnœa. On April 30th he began to complain of some more or less constant epigastric pain, worse after food, but this passed off in the course of the next week. Associated with this was severe diarrhœa, which, however, proved amenable to treatment, and his general condition a little improved. On May 5th he complained for the first time of discomfort on swallowing, the pain being referred to the latter period of the act of deglutition. On May 14th the pain on swallowing was much more definite and distressing, and from that time onwards he could only be persuaded to swallow by previously spraying the fauces with a 2½ per cent. solution of cocaine. It was noticed also that this gave no relief unless he *swallowed* some of the cocaine solution. From the date of appearance of the dysphagia he rapidly sank, and died on May 17th.

Post-mortem examination.—Unfortunately permission to make a complete examination could not be obtained from the relatives.

Lungs and pleuræ.—On opening the chest a left pyopneumothorax was found to be present. The visceral pleura on this side was considerably thickened, and a valvular opening at the apex of the lower lobe communicated with a small cavity, which in its turn opened into a medium-sized bronchus. The lung was much contracted. In both lobes were small cavities filled with caseous material, and the rest of the left lung was much fibrosed. On the right side the pleura was adherent at the apex, and the lung presented small, smooth-walled cavities at the apices of the upper and lower lobes. The remainder of these and the middle lobe were studded with grey racemose tubercles.

Larynx.—This unfortunately could not be examined, but when inspected twelve days before death early tuberculous disease was observed.

The *trachea* and *great bronchi* were markedly ulcerated. At the bifurcation of the trachea the cartilages were exposed and partly destroyed, but at no point had the disease actually perforated the wall, and the mediastinal tissues seemed to be uninvolved.

Glands.—The *bronchial* and *mediastinal* lymphatic glands were enlarged, but presented no macroscopic evidence of tuberculous infection.

The *lower cervical* glands appeared natural, and the *mesenteric* glands were enlarged but not caseous.

FIG. 8.

Showing the upper end of the œsophagus and the character of the tuberculous ulceration described. (Nat. size; from a drawing.)

The *pericardium* was natural, and the *heart*, beyond some degree of fatty infiltration of its walls, appeared to be normal.

The *liver* was enlarged, firm, and somewhat fatty.

The *spleen* and *kidneys* were natural.

The *right epididymis* showed a few caseating points, but the left was natural.

Alimentary canal.—The lower part of the ileum, the cæcum, the appendix, and the large intestine as far as the lower end

of the sigmoid flexure, showed numerous tuberculous ulcers. The rectum was natural.

Œsophagus.—The upper portion of this viscus could not be examined. Throughout the lower part of the upper third, and the greater part of the middle third, and involving almost the whole circumference of the tube for a space of three and a half inches, were very numerous ulcers. The tissue between these appeared to be infiltrated and to contain areas of caseation. Below this level a gradually decreasing amount of scattered ulceration was to be seen, and even at the lower end there were a few abrasions suggestive of ulceration. Though the ulcers presented a ragged appearance, and in many cases were freely interconnected, there seemed to be evidence of a series of separate foci of infection. When individual ulcers appeared they were roughly oval in shape, and lay with their long axes in the long axis of the œsophagus. They presented a rather sharply cut edge, which seemed in some instances to be a little undermined.

The loose areolar mediastinal tissue around the œsophagus appeared to be healthy, and there were no caseous glands in the immediate vicinity of, much less adherent to, that organ; so that extension in contiguity from without could at once be excluded as the source of infection. The fauces and pharynx were not examined *post mortem*, but during life no signs of ulceration had been detected in them.

Microscopic examination.—A section through one of the ulcers at the upper end of the œsophagus showed a somewhat infiltrated edge containing numerous typical tubercles with giant-cells, and also caseous and necrotic areas. The squamous epithelium lining the œsophagus ended abruptly at the edge of the ulcer. The floor was rough and densely infiltrated with small round cells, among which a few areas of caseation were visible, but no giant-cells. The ulcerative process had not proceeded very deeply into the submucosa, and was sharply bounded by a zone of fairly dense fibrous tissue which contained a few dilated vessels.

In every section examined typical tubercles were found only beneath the still intact epithelium at the margins of the ulcers.

Tubercle bacilli were found in fair numbers between the squamous epithelial cells and in the tuberculous formation of

the edge of the ulcer. In the actual base of the ulcer they were seen only in very scanty numbers. A section cut through the infiltrated but not actually ulcerated area, immediately above that of the preceding section, showed in the mucous membrane patches of infiltration and caseation, with numerous typical tubercles and giant-cells. In close proximity to, and in most cases in direct continuity with, these areas of caseation, appeared gaps in the epithelium and basement membrane.

In some such situations tubercle bacilli were found between and beneath the epithelial cells, a fact which seems to suggest a primary surface infection rather than a direct downward extension from pharyngeal ulceration. A section through the extreme lower end of the œsophagus showed an intact epithelium, and no signs of disease in the submucous or muscular tissue. In contrast to the microscopic appearances found in so-called aphthous ulceration of the œsophagus, there was in this case much less congestion and dilatation of the small vessels of the mucosa, much more round-celled infiltration, and a more sharply defined marginal limitation both in depth and extent. The extent of the fibrous tissue bounding the tuberculous ulceration suggested a considerable degree of chronicity in the progress of the disease.

Pathogenesis.

The source of infection of the œsophagus remains to be discussed. Flexner, and later, Cone, have classified tuberculosis of the œsophagus from this standpoint as follows:

	No. of cases recorded.
I. Instances in which the tuberculous process arises through continuity or contiguity of structure.	
a. From caseous bronchial glands . . .	19
b. By perforation of abscesses from tuberculous disease in neighbouring structures:	
i. Spinal caries	3
ii. Empyema	1
c. By extension downwards from tuberculous ulceration of the pharynx . . .	2
Total . . .	25

	No. of cases recorded.
II. Instances in which there exists in the œsophageal mucous membrane a previous lesion to be regarded as predisposing to the tuberculous infection.	
a. Thrush, with extensive ulceration . .	1
b. Traumatic ulceration, due to swallowing corrosive liquid, followed by stricture . .	1
c. Carcinoma of the œsophagus . . .	3
Total . . .	5
III. Instances in which the œsophagus is infected in the course of a general miliary tuberculosis . .	6
IV. Instances of the infection of the mucosa from tuberculous sputum where no previous lesion existed .	16

The figures in the column headed "Number of cases described" are taken from Cone's monograph in the 'Bulletin of the Johns Hopkins Hospital,' with the addition of cases described since to which references are given below. Two of the cases recorded by W. Bartlett, of St. Louis, appear to have been described in detail in two separate journals. The case now recorded might conceivably be placed under the headings I *c*, III, or IV. Of these, III can be excluded, as there were no evidences of miliary tubercle elsewhere, and the lesions of the œsophagus in recorded cases of this variety are described as being elevated dots and larger nodules in great numbers in the mucosa, none of which had ulcerated, and which, histologically, were shown to be lymph-follicles invaded by miliary tubercles. A section through such a follicle is figured by Cone in his monograph. It remains to decide whether the ulceration in this case arose from a spread of ulceration from the pharynx (I *c*), or a local infection by tuberculous sputum (IV). Owing to want of opportunity to examine the pharynx, the former cause cannot be excluded; moreover the ulceration certainly agrees with the published descriptions of this variety, in that it is deepest and most abundant at the upper end of the œsophagus, and that the ulcers have their long axis in a longitudinal direction, whereas in cases of local infec-

tion they are said to be often transverse. On the other hand, no lesions were found in the pharynx during life, while the presence of isolated ulcers gradually fusing as they extend, with bacilli between and beneath the epithelial cells in the intervening tissue, suggests the probability of a local infection through the sputum, which may well have had some additional secondary spread along neighbouring lymphatics.

REFERENCES.

1. *Flexner.*—'Johns Hopkins Hospital Bulletin,' vol. iv.
2. *Cone.*—Ibid., vol. viii.
3. *Bartlett.*—i. 'Annals of Otology, Rhinology, and Laryngology,' St. Louis, November, 1899. ii. 'Medical Review,' St. Louis, January, 1900.
4. *Edsall.*—'Transactions of the Pathological Society of Philadelphia,' vol. xviii.
5. *Beneke.*—'Deutsche Aerzte Zeitung,' Berlin, 1901, vol. i.
6. *Shattock.*—'Trans. Path. Soc.,' vol. liii.

January 6th, 1903.

10. *Diffuse carcinomatosis of the stomach and intestines.*

By A. W. NUTHALL and J. G. EMANUEL.

WE have recently had an opportunity of examining three cases of widely diffused malignant disease of the stomach and intestines, a condition which, so far as we have been able to ascertain, has not been previously described. In all the cases a long tract of the alimentary canal was affected, the stomach, the small and the large intestines being in each case the seat of a widely diffused carcinomatous infiltration. In every case the stomach presented the condition described as "leather-bottle stomach," either in whole or in part. Thus in Cases 2 and 3 the stomach was a typical leather-bottle stomach, while in Case 1 only the pyloric half of the stomach was affected in this manner. A similar growth to that affecting the stomach also involved the small and large intestines to different extents in the different cases. In the intestines the growth seemed to start at the attached border of the mesentery or its homologues —viz., the mesocæcum, mesocolon, mesosigmoid, and mesorectum

—and to infiltrate the wall of the bowel for a varying distance towards its free border, in some parts entirely encircling the bowel and in other parts only spreading into the bowel for a short distance from its attached border. In places where the growth had infiltrated the entire circumference of the gut it was thickest at the attached border and gradually became thinner towards the free border. In Case 1 the parts affected were the pyloric half of the stomach, the small intestine in places, and the entire colon, while the cæcum was free from growth; in Case 2 the entire stomach was infiltrated, the small intestine in places, and the whole of the colon, the cæcum again being free; while in Case 3 the entire stomach, the small intestine in places, the cæcum, the colon, and the rectum were infiltrated with growth. To the colon in all the cases, and to the cæcum and rectum in Case 3, the terms "leather-bottle" colon, cæcum, and rectum respectively might be fittingly applied. In all the cases the growth had spread for a short distance in between the two layers of the mesentery and the mesocolon, and in Case 3 the mesocæcum and the gastro-hepatic omentum were similarly affected. In Cases 1 and 2 the cæcum and mesocæcum were unaffected. We are not sure of the condition of the gastro-hepatic omentum in Cases 1 and 2, as no note was made of these parts at the time of the *post-mortem* examinations. In all the cases the great omentum, the mesenteric and retro-peritoneal glands were free from growth. The fundus of the gall-bladder in Case 1 was infiltrated with carcinomatous growth to the thickness of one eighth of an inch, and there was a small metastatic deposit in one of the kidneys of this case; but, with these exceptions, there were no metastatic growths in any one of the three cases. In all the cases there was in no part of the stomach or intestines any sign of ulceration of the mucous membrane, and until microscopic sections were made it was not clear where the growth had originated. The result of this widely diffused malignant disease was to cause stenosis at one or other part of the alimentary tract and sometimes at more than one part in the same case. Thus, the patient in Case 1 died from perforation of the cæcum behind a stenosis in the ascending colon; in Case 2 the patient had gastro-jejunostomy performed for pyloric obstruction; while in Case 3 there was some hesitation between performing a gastro-jejunostomy for pyloric obstruction or

an inguinal colotomy for rectal obstruction. In this case the colotomy was finally decided upon, but the autopsy showed that a gastro-jejunostomy was just as much indicated.

Case 1 was that of a female; Cases 2 and 3 were those of males. The ages were 27, 38, and 56 years respectively. Ascites was present in Case 3, but absent in Case 2, while the presence of the septic peritonitis in Case 1 made this condition uncertain.

The following is a brief record of the clinical aspect of each case with details of the *post-mortem* examinations:

Case 1.—A woman aged 27 years was admitted into the General Hospital, Birmingham, on June 8th, 1901, with general septic peritonitis. Her previous health had been good until twelve months before her admission, and during this time she had suffered from anæmia and debility, and indefinite abdominal pain of an intermittent colic-like nature. A week before her admission symptoms of intestinal obstruction supervened, and she was received into the hospital with signs of general peritonitis. She died two hours after her admission, during the administration of an anæsthetic, of asphyxia from regurgitation of stomach contents into the larynx.

Post-mortem report.—Body thin. No external glandular enlargements. Abdomen much distended and containing free gas and about three pints of turbid, purulent fluid, mixed with fæcal matter. There was a general acute septic peritonitis, the entire peritoneum being covered by a thick fibrinous exudation, loosely glueing the coils of intestine together. The peritonitis was due to the perforation of a stercoral ulcer situated in the cæcum. The cæcum was dilated and thinned owing to its lying above an obstruction in the ascending colon. The œsophagus was healthy. The stomach was small and was much thickened at the pyloric end, the fundus and cardiac end being of natural thickness. The thickening was due to an infiltrating growth of the wall of the stomach starting at the pylorus, where it was one third of an inch in thickness, and spreading for about four inches into the main portion of the stomach, gradually thinning away into the normal stomach wall. There was no stenosis of the pylorus. The mucous membrane and the serous coat of the stomach were quite intact, and were not apparently

affected by the growth. The duodenum was free from growth, but the jejunum, ileum, and colon showed the presence of a similar growth to that in the stomach wall. In the small intestine the growth was present only at certain places along the mesenteric border of the bowel, and spread only for a short distance into the wall of the bowel, but the colon was affected throughout its length, and here, too, the entire circumference of the bowel was infiltrated. Everywhere the mucous membrane of the intestine was intact and showed no ulceration. The lumen of the small intestine was normal, but that of the colon was much encroached upon in places by the infiltrating growth. The greatest narrowing occurred in the ascending colon and was so marked that the cæcum was much thinned and dilated, and contained in its wall a perforated stercoral ulcer. The great omentum was free from growth. There were no enlarged mesenteric or retro-peritoneal glands. The growth, however, penetrated for a short distance between the two layers of the mesentery and mesocolon. The liver weighed 56 oz., and was fatty. The gall-bladder was contracted, thick-walled, and empty. It was the seat of a similar infiltration to that in the stomach and intestines which had started at the fundus and terminated abruptly at the beginning of the cystic duct. The spleen was soft and small. The kidneys together weighed 10 oz., and one of them contained in the cortex a small ill-defined pale patch which, on microscopical examination, proved to be a metastatic deposit of the new growth. The supra-renals were healthy, as were also the bladder and urethra, the uterus and the adnexa. There were no metastases other than the infiltration of the fundus of the gall-bladder, and the growth in one kidney.

Case 2.—A man aged 38 years was admitted into the General Hospital, Birmingham, on October 3rd, 1901, complaining of epigastric pain of about ten weeks' duration and of vomiting after meals during the past month. His history prior to May, 1900, was not obtainable. At that date, however, he had an attack of severe pain in the right side of the abdomen and a right subphrenic abscess was found and was drained by an abdominal incision. The cause of the abscess was not ascertainable at the time of the operation, or even later at the autopsy. He was free from pain after

this operation till ten weeks before his admission, when a recurrence of the gastric symptoms appeared. He had severe epigastric pain which was worse after meals, and occasional vomiting. The pain used to come on periodically in attacks of great severity, lasting for several hours and leaving the patient very exhausted. On admission into the hospital he was very emaciated, and his general condition one of marked asthenia. The pain was constant, he vomited frequently almost immediately after taking food, and consequently was only able to take very small quantities of liquid food at a time. The bowels were opened with difficulty—only by enemata. On October 7th, 1901, anterior gastro-jejunostomy was performed, a Murphy's button being used. He sank and died on October 10th.

Post-mortem examination.—Body very emaciated, no œdema, jaundice, or external glandular swellings. There was an old laparotomy scar through the right rectus abdominis close to the costal margin (the incision through which the subphrenic abscess had been drained in May, 1900), and there was a recent wound in the middle line (through which the gastro-jejunostomy had been performed). On opening the abdomen the upper part of the peritoneal cavity was found to be obliterated by an entangled mass of firm fibrous adhesions, and the jejunum was seen to be anastomosed to the anterior wall of the stomach by a Murphy's button. The union was good, the button was *in situ*, and there were no signs of recent peritonitis. The vermiform appendix was healthy but very long, and passed up over the right kidney embedded in firm adhesions and its tip lay almost touching the fundus of the gall-bladder. The œsophagus was healthy. The stomach was very small and contracted, and its walls much thickened—the leather-bottle stomach. The thickening was seen to be due to a submucous infiltrating growth of a pearly homogeneous glistening appearance. The growth was thickest at the pylorus, and here it measured one third of an inch in depth; traced towards the fundus it became gradually less and less thick. The pyloric orifice was narrowed, barely admitting the tip of the little finger. The mucous membrane of the organ was everywhere intact and presented no signs of ulceration, either recent or old. The duodenum was healthy. The mesentery of the jejunum and ileum presented many small nodular thickenings situated between the

two layers of the peritoneum close to the bowel, and spreading in places into and around the wall of the bowel, and causing a decided thickening of the bowel at these places. The cæcum was thin and a little dilated; the colon was thick-walled, but there was no narrowing of the lumen. The thickening of the colon was due to an infiltration of the wall by a pearly homogeneous glistening growth similar in appearance and in distribution to that affecting the stomach. The growth was thickest at the attachment of the colon to the mesocolon, and it became thinner as it was traced towards the free surface of the colon. There was no ulceration of the mucous membrane of the intestine. The omentum was free from growth, and there was no enlargement of the mesenteric or retro-peritoneal glands. There were no metastases. Each kidney was in an advanced condition of hydronephrosis, due to the impaction of calculi in the pelvis. The other organs were healthy.

There was nothing found at the *post-mortem* examination to account for the subphrenic abscess drained during life, although the adhesions in the upper part of the abdomen were the probable result of this collection of pus. There were no symptoms during life suggesting the presence of renal calculi; in fact, these and the resulting hydronephrosis were quite unexpectedly found at the autopsy.

Case 3.—A man aged 56 years was admitted into the General Hospital, Birmingham, on September 23rd, 1901, complaining of severe abdominal pain, of increasing difficulty in passing his motions, and of distension of the abdomen. Prior to these symptoms, which were of gradual onset and of about eight months' duration, the patient had had good health. On admission into the hospital he was very emaciated and very weak. The abdomen was greatly distended and an attempt was made to relieve the distension by tapping, but only about 20 oz. of almost clear ascitic fluid was obtained by syphonage, and the distension remained evident. No tumour was definitely felt by palpation, but *per rectum* an obstruction encircling and almost occluding the bowel was found. No ulceration of the mucous membrane was felt in the rectum, nor any growth projecting into the lumen. The condition suggested a fibrous stricture. When the question of more radical treatment was discussed there was hesitation

as to whether the patient would be more relieved by a gastro-jejunostomy than by a colotomy. So prominent a symptom was epigastric pain immediately after taking food that malignant disease of the stomach could not be dismissed. It was decided, however, to treat the rectal obstruction which was undoubtedly present, rather than to attempt to relieve the problematical condition of the stomach. The subsequent autopsy revealed that either operation alone would have been ineffectual. Colotomy was performed on September 28th. Ascitic fluid escaped freely at the operation, and leaked constantly from the wound until the death of the patient, which occurred three weeks later from gradual exhaustion, on October 19th.

Post-mortem examination.—The body was extremely emaciated. There was no jaundice, no œdema, nor any external glandular swellings. There was a colotomy wound in the left iliac region into which the sigmoid flexure opened. On opening the abdomen about three pints of hæmorrhagic fluid escaped. The peritoneum was acutely inflamed and covered with a fibrinous exudation, matting the coils of intestine loosely together and peeling easily off the intensely injected surface beneath. The œsophagus was healthy. The stomach was small and contracted and its wall greatly thickened throughout—the leather-bottle stomach. The duodenum and jejunum were thin and somewhat dilated. The walls of the ileum were thickened at places. The cæcum was very small and contracted, and its walls greatly thickened, closely resembling the leather-bottle stomach in appearance. The colon was throughout its length contracted and thick-walled, the hepatic and splenic flexures and the rectum being so much stenosed that they would hardly admit the little finger. There was no ulceration of the mucous membrane of any portion of the stomach or intestines. The thickening of the parts mentioned was due to infiltration of the walls of the gut by a homogeneous-looking growth starting at the attachment of the gastro-hepatic omentum, mesentery, meso-cæcum, mesocolon, and mesorectum to the various viscera (stomach, small and large intestines), and spreading into the wall of the bowel in the submucous layer. In places it entirely encircled the bowel, but everywhere was obviously thicker and more definite at the attached border and gradually shaded off to the opposite free border of the bowel. The gut was not

uniformly affected with the growth. Along the small intestine it could be better felt than seen as small nodular thickenings at the attached border of the bowel. In the large intestine the thickenings were in places very conspicuous, and gave rise to the stenoses of the hepatic and splenic flexures and of the rectum mentioned above.

The great omentum was free from growth. There was no infiltration of the mesenteric or retroperitoneal glands. There were no metastases. The other organs were healthy.

The accompanying table is a summary of the important features of these cases.

Case.	Sex.	Age.	Prominent symptoms.	Provisional Diagnosis.	Treatment.	Approximate duration.	Site of growth.	Metastases.	Ascites.	Site of obstruction.
I	F	27	Anæmia; debility; abdominal pain	General peritonitis	Laparotomy	12 months	Pyloric end of stomach; small intestine (in places); whole of colon	Gall-bladder; kidney	? (free gas and fæcal fluid in peritoneal cavity)	Ascending colon.
II	M	38	Epigastric pain; vomiting	Gastric ulcer	Gastro-jejunostomy	3 months	Whole of stomach; small intestine (in places); whole of colon	None	No ascites	Pylorus.
III	M	56	Chronic constipation, with abdominal pain and distension	Fibrous stricture of rectum and ? malignant disease of stomach	Colotomy	8 months	Whole of stomach; small intestine (in places); cæcum; colon; rectum	None	Ascites	Pylorus; cæcum; hepatic flexure; splenic flexure; rectum.

Microscopical characters.—In all the cases the characters of the new growth were identical in the main, only differing in minor details. We found that the growth was a glandular carcinoma arising in the deeper layers of the gastric mucous membrane and undergoing colloid degeneration. Our conclusions were based on the study of sections from the following parts :—

In Case I.—(1) Stomach wall, T. S. (transverse section) taken at the junction of the infiltrated part with the healthy part, a point about 4 inches from the pyloric end.

(2) Ileum, T. S. taken at junction of bowel to mesentery, including the mesenteric attachment.

(3) Colon, T. S. of the free unattached portion of the wall away from the mesocolon.

(4) The metastasis in the kidney.

(5) The infiltrated fundus of the gall-bladder.

In Case II.—(1) Stomach, T. S. of the thinnest part of the infiltrated wall.

(2) Ileum, T. S. of entire intestine.

(3) Splenic flexure, T. S. of entire intestine.

In Case III.—(1) Stomach, T. S. of thinnest part of infiltrated wall.

(2) Cæcum, T. S. of free surface.

(3) Rectum, T. S. of free surface.

In all these sections growth of identical nature and distribution was found, but the colloid degeneration was variously advanced in the different cases, and of varying degree in the different parts of the same case. In all the distribution of the growth was identical. It formed a very thick continuous layer occupying the submucosa, and another less thick but still continuous layer occupying the subserosa, and these two layers of growth were united to one another by strands of growth of varying thickness, splitting up the muscular layers of the stomach and intestines into bundles of muscular fibres of varying size. In the sections of the small and large intestines of these cases the muscularis mucosæ and the mucous membrane beyond were for the most part intact; occasionally, however, a mass of glandular carcinoma was found occupying the deeper parts of the mucous membrane and penetrating through the muscularis mucosæ to become continuous with the main mass of growth in the sub-

mucosa. In the stomach sections, however, while the growth had the above general distribution, it could be seen to arise in the deeper layers of the mucous membrane as a typical glandular carcinoma, to penetrate the muscularis mucosæ and to become continuous with the main mass of growth in the submucosa, with which again the subserous layer of growth was joined by strands of growth splitting up the muscular coat.

As we have said, the amount of colloid degeneration varied in the different cases and in the different parts of the same case. In any particular section the degeneration was seen to become more advanced as the growth was traced outwards from the mucous membrane to the serous coat, so that in every case the growth occupying the subserosa was more degenerated than the layer of growth in the submucosa of the same part. Many of the sections showed the different stages of colloid degeneration in a very beautiful manner. Throughout the sections the cells of the growth stained but faintly. They showed great inequality in size, and there was a general tendency to increase in size as one passed from the mucosa to the serosa. With this increase in size there was a marked tendency to vacuolation and granularity of the protoplasm with displacement and distortion of the nucleus, till in the serosa large spaces filled with colloid material, and containing only the *débris* of pre-existing cells, were met with. This degenerative change, which we believe is of a colloid nature, was only appreciable microscopically. There was nothing in the macroscopical appearance of the stomach or intestines to suggest such a change. Everywhere the infiltrated parts of the stomach and intestines were of leathery hardness, and we anticipated a fibrous infiltration of the parts rather than the carcinomatous growth which we found. In fact, when the *post-mortem* examinations were first made, we thought we had the condition described in Osler's 'Medicine' (proliferative peritonitis), in which a thickening of the peritoneum is found associated with cirrhosis of the cæcum and ascending colon, or of the stomach. Some of the sections in which the degeneration was so advanced that practically no definite epithelial cell elements remained—the tissue appearing as a fibrous meshwork, enclosing apparently empty interspaces—helped to bear out the opinion formed on a naked-eye examination only, that the entire process was a

diffuse fibrosis. A consideration of sections, however, from different parts and the evidence they afforded of different stages of the same degenerative process have led us to our final conclusion that these were cases, not of a diffuse fibrosis, but of a diffuse carcinomatosis undergoing colloid degeneration. This degeneration was most marked in Case 2 and least marked in Case 1.

In Case 2 the degeneration was more advanced in the splenic flexure than in the ileum and more advanced in the ileum than in the stomach. In Case 3 the degeneration had an exactly opposite distribution, being more advanced in the stomach than in the cæcum, and more advanced in the cæcum than in the rectum; while in Case 1, in the stomach the degeneration was only present in the subserous layer of growth, while in the ileum and colon the submucosa as well as the subserosa showed marked degeneration.

We have referred at some length to the presence of the degeneration in these growths, because it so masks the true (carcinomatous) nature of the growth in many of the sections that when we showed specimens of these cases at the meeting of the Pathological Society of London, held on April 29th, 1902, we were altogether in doubt as to the exact nature of the growth, and we suggested that they might be endotheliomata. A more careful study of the sections, however, has brought us now to the conclusion that they are carcinomata arising in the deeper layers of the gastric and intestinal mucous membranes undergoing colloid degeneration. We do not seem to have been alone in describing these specimens as endotheliomata, as the 'Centralblatt für Gynäkologie' shows. On page 1109 in No. 42 (October 18th, 1902) we read the following:

"Many so-called endotheliomata of the intestines are only metastases of, for example, scirrhus of the stomach."

We have not been able to find any account of such wide-spread carcinomatous infiltration of the stomach, the small and the large intestine, in the literature of malignant disease of the intestinal tract, and so we have reported these cases in some detail.

We wish to thank the staff of the General Hospital, Birmingham, for permission to publish these cases.

November 17th, 1902.

11. *On biliary cirrhosis of the liver, with and without cholelithiasis.*

By F. Parkes Weber.

A good many cases of various forms of biliary cirrhosis have been described in England, either separately or included in papers on hepatic cirrhosis in general, but without doubt the chief part of the literature on this subject is French. I need only instance the observations of Hanot, Charcot, Hayem, and the repeated publications by Gilbert and his pupils, culminating in the recent collective work by Lereboullet.[1] In England, apart from work on experimental biliary cirrhosis by Wickham Legg,[2] and by Vaughan Harley in conjunction with W. Barratt,[3] the most important contributions are probably those contained in the various papers on diseases of the liver by H. D. Rolleston.[4]

My definition of biliary cirrhosis is: "Any cirrhosis of the liver originating from disease of the biliary ducts or obstruction to the outflow of bile." As I shall later on point out, I believe that individual tendency, or "tissue proclivity," plays a part in the development of this cirrhosis, as it does in the development of almost all pathological changes. Not every one with chronic disease in the bile-ducts develops biliary cirrhosis.

In deciding what cases of cirrhosis of the liver are to be regarded as biliary cirrhosis, too much importance must not be attached to the histological findings. The apparent increase of biliary canaliculi may be very well marked in ordinary cirrhosis, and may be absent in biliary cirrhosis, whilst in biliary cirrhosis the unilobular distribution of the fibrotic tissue is often not nearly so typical as one would suppose from the term mono-

[1] 'Les Cirrhoses biliaires,' Paris, 1902.

[2] "On the Changes in the Liver which follow Ligature of the Bile-duct," 'St. Bart.'s Hosp. Reports,' 1873, vol. ix, p. 161.

[3] "The Experimental Production of Hepatic Cirrhosis," 'Journal of Pathology,' 1901, vol. vii, p. 203.

[4] See his article on "Diseases of the Liver" in the 'Encyclopædia Medica,' vol. vi; on the "Etiology of Cirrhosis of the Liver," in the 'Quarterly Medical Journal,' July, 1899; and on "Cirrhosis of the Liver in Children," in the 'Clinical Journal,' September 9th, 1896.

lobular (better, "unilobular"), or perilobular (better, "interlobular" or "circumlobular") cirrhosis having been occasionally used as a synonym of biliary cirrhosis. In this respect it must be remembered that Charcot and Gombault,[1] who originally introduced the term "monolobular" cirrhosis, wrote: "Toutefois, cette régularité est loin de s'observer dans tous les cas et sur tous les points." Even in experimental biliary cirrhosis in animals, as that produced by Vaughan Harley and Barratt,[2] the distribution of the anatomical change is by no means quite regular. Professor Vaughan Harley kindly informs me that at the end of four to six months, when the cirrhosis was slight, the distribution was tolerably uniform, but that in the later cases, after twelve to sixteen months, it was markedly irregular. In biliary cirrhosis in the human subject, I believe that the changes seen by the microscope in the liver are always irregular in distribution, excepting in cases where the disease is just commencing. The changes, however, are probably fairly uniform, and the cell-infiltration is probably confined to the interlobular spaces in cases also of ordinary cirrhosis at the commencement of the disease. Moreover, "mixed cases" may occur—that is, cases in which the hepatic cirrhosis is partly of the ordinary kind (*i. e.* having its origin in connection with the portal blood-vessels), and only partly biliary (*i. e.* having its origin in connection with the minute bile-vessels). It has been suggested that in late stages of biliary cirrhosis,[3] owing to digestive and metabolic disturbance set up by the hepatic disease, a toxæmic condition is induced in which, by the poisons carried with the blood-stream to the liver, an ordinary multilobular cirrhosis is added to the original biliary cirrhosis.

I need scarcely mention that both biliary cirrhosis and ordinary cirrhosis may be "hypertrophic" or "atrophic," though the former is more often "hypertrophic" than the latter, and is seldom really "atrophic," if the latter epithet be taken to imply that the weight of the diseased organ is actually below the normal standard. It is certainly a mistake to use the term "hypertrophic cirrhosis" as synonymous with biliary cirrhosis,

[1] "Contribution à l'Étude anatomique de différentes Formes de la Cirrhose du Foie," 'Archives de Physiologie,' 1876, p. 469.

[2] Loc. cit.

[3] *Vide* Rolleston, 'Encyc. Med.,' loc. cit.

or even to use the term "hypertrophic biliary cirrhosis" as synonymous with biliary cirrhosis, as is still not rarely done in England and Germany.[1] The history as well as the anatomical features must be taken into consideration in deciding which cases are to be termed biliary cirrhosis, and so separated off from the many cases of ordinary cirrhosis due to alcohol, etc.

In the present paper on biliary cirrhosis I have first taken the cases associated with cholelithiasis,[2] and then the cases in which no evidence of cholelithiasis or previous cholelithiasis could be detected. The illustrative cases alluded to are partly from English and partly from foreign sources.

PART I.—CASES OF BILIARY CIRRHOSIS WITH CHOLELITHIASIS.

CASE 1.—Mrs. J. D—, aged 52 years, suffered more or less from jaundice during the last seven years of her life. At one time she was very greatly relieved by operative treatment, but it is very doubtful whether at any time the jaundice absolutely cleared up, for the pruritus persisted from the commencement of her illness in 1895 to her death in 1902.

I first saw her in December, 1895. At that time she was deeply jaundiced and emaciated. The jaundice and itching had already lasted several months, and at times she had had pain in the right hypochondriac region. Considerable uniform enlargement of the liver was made out, but the gall-bladder could not be felt. There was a tendency to diarrhœa, as there often is, both in cases of chronic hepatic and of chronic renal disease. Neither at this time, nor at any time subsequently, was there reason to suppose that alcohol or syphilis[3] played a

[1] I do not, of course, use the term "biliary cirrhosis" to include all cases of non-alcoholic and non-syphilitic cirrhosis, even when they occur in children. Non-alcoholic cirrhosis may certainly be of the ordinary, alcoholic, type.

[2] To the cases of biliary cirrhosis with obstructive cholelithiasis should perhaps be added a few cases of biliary cirrhosis with obstruction in the large ducts from tumours and causes other than gall-stones, such as have been included by Dr. W. W. Ford in his article on "Obstructive Biliary Cirrhosis," 'American Journ. Med. Science' (January, 1901, p. 60). For the term "obstructive biliary cirrhosis" I would substitute "biliary cirrhosis from obstruction in the large ducts," since I believe that even the cases of biliary cirrhosis without obstruction in the large ducts (Hanot's disease) are to some extent examples of obstructive biliary cirrhosis, the obstruction being in the minute ducts.

[3] Unless, indeed, the extreme atheromatous changes found in the aorta at the necropsy could be taken as evidence that there had been syphilis.

part in the patient's case. Saline treatment was tried with care, but no improvement followed. The case seemed possibly one of cholelithiasis, and I thought of the advisability of an operation. Mr. Lockwood kindly took the patient into the Great Northern Hospital, and I have to thank him for allowing me to be present at the operation, and for information as to the result. At the operation, which was performed on March 7th, 1896, about twelve months from the commencement of the jaundice, the liver was found to be enlarged; it was very dark, and, by its peculiar crinkled appearance when squeezed, seemed to have already undergone some fibrotic change. The gall-bladder was not distended, but contained several faceted calculi, some of which were rather friable, together with a pale greenish mucous fluid. Mr. Lockwood felt something hard at the head of the pancreas, which he thought was due to a calculus in the common bile-duct. No calculi could be felt in the cystic duct. For certain important reasons connected with the state of the patient, Mr. Lockwood determined only to do a cholecystostomy on that occasion. At first no bile came away, but two or three weeks after the operation a regular flow of bile from the fistula was established, sometimes green in colour, sometimes brown, and the jaundice gradually began to clear up. The biliary fistula was allowed to close at the latter end of 1896, and the patient's general condition appeared very good. So great, indeed, was the relief afforded that the patient did not come for a second operation, which Mr. Lockwood had proposed to do for the purpose of removing the calculus from the common bile-duct. It seemed even uncertain whether this calculus was still present. However, she certainly suffered occasionally from jaundice, and it is doubtful whether the jaundice ever absolutely cleared up. She always had more or less pruritus, and xanthoma appeared in the latter part of 1896. The xanthoma was first noticed in the eyelids, but afterwards the elbows and neck were affected. The urine and fæces, however, were said usually to have been natural in colour. She was able to continue her work (washing clothes) till about February, 1901, when the skin became yellower and the urine darker.

When I saw her on April 25th, 1901, she was moderately jaundiced, and pruritus and scratching were evidenced by a great number of scabs. Besides the yellowish tinge of icterus

there was a certain amount of dusky pigmentation of the skin, such as may be noticed in most cases of very chronic jaundice; this was most obvious on the neck, forearms, and abdomen. On one thigh there was discoloration from a bruise, which was said to have arisen without any known traumatism. There were the ordinary raised circumscribed patches of xanthoma at the inner parts of the eyelids, larger raised patches about the elbows, and a few small spots about the axillæ. On each side of the neck there was a diffuse area of xanthoma, which was level with the rest of the skin; these patches had a somewhat vitiligo-like appearance owing to the fact that they were not raised, and that the skin of the neck around them was, as I have already mentioned, somewhat abnormally pigmented. Examination of the thoracic organs showed nothing abnormal. Pulse 78, regular. The upper border of the hepatic dulness was at the fifth rib in the right nipple line; the hard lower edge of the liver could be felt on the right close to the anterior superior iliac spine; in the middle line it was a little above the umbilicus. The spleen was likewise much enlarged; the lower border could be felt just above the left anterior superior iliac spine, and the upper margin of the dulness was at about the ninth intercostal space in the mid-axillary line. The urine was of specific gravity 1·010, clear, of neutral reaction, containing a trace of albumen,[1] free from sugar, and giving a moderate Gmelin's reaction for bile pigment. In May, 1901, the patient seemed better again, and rather less jaundiced.

In August, 1901, her case was diagnosed at one of the large London hospitals as a case of malignant disease of the liver, probably commencing in the gall-bladder in connection with

[1] It is perhaps only in the *most extreme degrees of jaundice* with chronic obstruction in the common bile-duct that the urine gives the *very marked* reaction for a mucinoid substance or nucleo-albumen, to which I alluded in 'Trans. Path. Soc. London,' 1900, vol. li, p. 176, and which is probably of bad prognostic significance. On the other hand, in all or nearly all cases of jaundice with complete obstruction to the escape of bile (even when of relatively short duration), casts can be found in the urine, if carefully searched for, though albumen be absent. These casts may contain pigment granules and pigmented cells, but have no special prognostic significance. Nothnagel ('Deut. Arch. für klin. Medicin,' 1874, vol. xii, p. 326), thought that in every marked case of jaundice, whatever the cause of the jaundice may be, casts appear in the urine. Cf. Dr. P. S. Wallerstein, "Ueber reine Cylindrurie bei künstlich erzeugter Gallenstauung," 'Berliner klin. Wochenschrift,' 1902, No. 14, p. 310.

cholelithiasis. But the patient was able to go on with her work. At the end of March, 1902, however, the jaundice deepened again, and when I saw her in April, 1902, her condition seemed much the same as in April of the previous year, except that the jaundice was probably more marked. There was a systolic murmur over the pulmonary area of the heart. The patient was admitted to the German Hospital in July, 1902, when she seemed very cachectic, but had a fair appetite. The xanthoma had probably not diminished, as it has been said to in some cases of chronic hepatic disease, but it had, I think, become less marked, owing to general pigmentary and degenerative changes in the skin. In July some dulness was noted at the base of the right lung, and in the latter part of the month there was a little cough and bloody sputum, but on the whole the general condition seemed again to improve a little. On the morning of August 14th, however, the temperature, which since patient's admission had never been elevated, rose suddenly to 102° F. Pulse 100. Slight dyspnœa. There was dulness at the back of the right lung, which an exploratory puncture showed to be due to a very bile-stained serous effusion in the pleural cavity. The left leg above the ankle was reddish, somewhat swollen, and tender. A painful swelling about the ankle had been first noted on the previous day (August 13th). On August 16th the left leg up to the knee was bluish, and gangrene seemed to be threatening. Fever continued. Death occurred on August 17th, 1902.

Necropsy.—The heart weighed 12 oz., and showed slight hypertrophy of the left ventricle, but no valvular disease. The whole of the aorta and both common iliac arteries were extremely atheromatous, and this probably explained the threatened gangrene of one limb before death. The right pleural cavity contained bile-stained serous fluid. In one of the lungs there was what seemed to be a not quite recent infarction. The kidneys together weighed 14 oz.;[1] they seemed fairly

[1] Thus the weight of the kidneys was somewhat above the average. I believe that in most cases of chronic hepatic disease the kidneys, if not independently diseased, are above the average in weight; and, conversely, in most cases of chronic renal disease the liver, if not independently diseased, is above the average in weight. The explanation is probably that in the former class of cases extra excretory work is thrown on the kidneys, and in the latter class extra work is thrown on the liver. In cases of chronic jaundice the continual

healthy, and the capsules stripped readily. The pancreas, macroscopically and microscopically, appeared normal. The *spleen* was large and rather soft, as it generally is in old cases of biliary cirrhosis; it weighed 36 oz. The capsule was a little thickened in places from old perisplenitis. From microscopic examination it appeared that the increase in size of the organ was due to engorgement with blood and to a simple hyperplasia of the pulp; there was, however, a slight relative increase in the amount of fibrous tissue, especially about the Malpighian corpuscles.

The *liver* (weight about 76 oz.) was enlarged, greenish yellow on section, and much cirrhosed. The surface was somewhat granular, with a few soft knobs,[1] but not nearly sufficiently puckered up to have a "hobnail" appearance. There was no malignant disease. There was dense scar tissue at the site of the old cholecystostomy wound. The gall-bladder was contracted, containing a little pale mucus. The lumen of the cystic duct was obliterated. Bile was seen oozing out of the papilla in the duodenum. The hepatic and common bile-ducts were both considerably dilated, and freely movable in the cavity formed by their dilated channels a solitary black kidney-shaped gall-stone was found, together with bile and a few sandy particles. The gall-stone measured 12 × 9 × 5 mm., and its surface, though not polished, was not very rough. This stone had probably, I think, been in the choledochus since the commencement of the illness. Microscopically the liver presented the appearances of irregular multilobular cirrhosis, though possibly

excretion of bile must throw extra work on the kidneys, and, I believe, the kidneys of persons with chronic jaundice from any cause become both "functionally," if I may say so, and organically hypertrophied. Recently I gave one decigramme of methylene blue to two patients with very chronic jaundice, and found that their urines became free from the blue colouring matter sooner than did the urines of healthy persons who took a similar dose for purposes of control at the same hour. The methylene blue was apparently excreted at a quicker rate by the patients, especially one of them, with chronic jaundice than by healthy persons. I am not sure whether this observation corresponds to what has been found by others; and the methylene-blue test is, it must be admitted, for many reasons unsatisfactory.

[1] Some of these little knobs were probably of the nature of regenerative hyperplasia or adenomata. Cf. H. Fraser's paper on "Multiple Adenomata in Cirrhosis of the Liver" ('Virchow's Arch.,' 1901, vol. clxv, p. 540), giving references to other literature on the subject. See also later foot-note.

the distribution of the fibroid tissue was more uniform, and in some parts more approaching a true unilobular arrangement than in cases of ordinary cirrhosis. In other words, the fibroid meshwork was finer and more regular than is usual in ordinary cirrhosis. But this was more obvious by naked-eye examination of the cut surface of the organ than by microscopical examination. The liver-cells over large portions of the sections were badly preserved, and their nuclei did not stain well. The fibroid tissue, which looked swollen up, showed in parts a good deal of recent small-cell infiltration. There was no obvious increase of bile canaliculi; on the contrary, it seemed as if many of the little ducts had been obliterated; typical duct-epithelium

FIG. 9.

A section of the liver from Case 1, showing the macroscopic appearance.

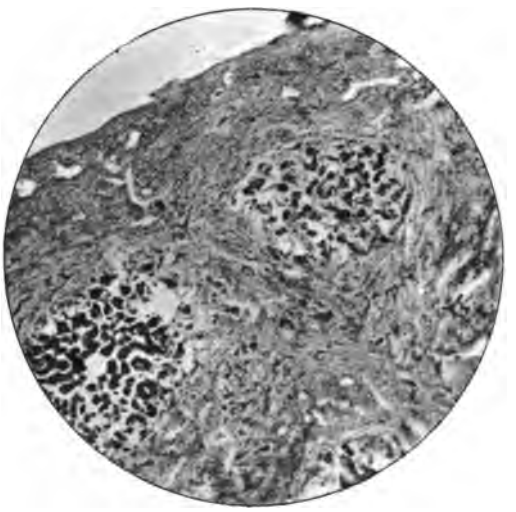
seemed to be almost absent; but these appearances may have been partly of *post-mortem* origin, or due to imperfect staining.[1] The liver-cells contained fine pigment granules, and apparently less fat than the cells in most cases of ordinary cirrhosis. There was likewise pigment to be seen here and there in the bands of scar tissue. Clumps of bacteria, deeply stained by Gram's method, probably a rapid cadaveric growth, were seen scattered about in the sections. I have to thank Mr. S. G. Shattock

[1] Yet these appearances may have some significance, as they are confirmed by what was found in my previous case (Case No. 2), and in some other cases (*vide* Cases Nos. 6 and 8). Increase of bile canaliculi is probably a more constant phenomenon in cases of Hanot's disease (see later) than in biliary cirrhosis with cholelithiasis.

for helping me in the microscopic examination of the sections.

CASE 2.—This case occurred several years ago.[1] The patient, Mrs. M. L—, aged 55, suffered more or less from jaundice during the last four years of her life. There was no history of previous attacks of jaundice, nor of syphilis, nor of alcoholism (?). A friend connected the onset of the illness with troubles following her husband's death. She had had no definite biliary colic, but had had pain in the left side. There were occasional exacerbations characteristic of the chronic jaundice associated with

FIG. 10.



Showing the microscopic appearances described in the liver of Case 2. (× 50.)

cholelithiasis. When I saw her first in November, 1894, the jaundice was deep; there was ordinary raised xanthoma of the eyelids, and on each side of the neck there was a diffuse area of xanthoma which, as in Case No. 1, was level with the surrounding skin of the part. Pruritus was troublesome. The liver was hard and uniformly much enlarged, and there was no ascites. In November, 1895, the patient was readmitted in a condition of general weakness and prostration. The skin appeared darker, as if more pigment had been deposited in it. The

[1] I gave an account of it in 'Brit. Med. Journ.,' April 25th, 1896.

pruritus had almost ceased. Some ascites could be made out, but there was no dilatation of veins over the front of the abdomen. The fæces were colourless, often loose, and accompanied by a little blood. The urine contained much bile pigment. There was great œdema of the lower extremities towards the end. The temperature never reached 100° F. Coma gradually supervened before the patient's death (December 24th, 1895).

At the *necropsy* the liver weighed 54 oz.; its substance was tough, its surface granular, and its colour greenish. The gall-bladder was rather dilated and hypertrophied, and contained a thin, faintly greenish fluid; the cystic and hepatic ducts were pervious. The common bile-duct was dilated, and near its orifice, in the diverticulum of Vater, were two black gall-stones, the larger one having the size of a small cherry-stone. Fluid could, however, be squeezed out by the bile-passages into the duodenum. This case resembles No. 1 in many respects, but especially in the small size of the gall-stones, which at the time of death were insufficient, unless by a ball-valve action, to cause complete obstruction to the outflow of bile. The microscopic preparations of the liver, which I still possess, so resemble those from Case No. 1 that I need not repeat what I said under that heading. The spleen likewise, as in Case No. 1, was uniformly enlarged and rather soft; it weighed 20 oz.

Case 3.—The following case has been described by Dr. C. M. Chadwick:[1]—The patient was a woman, aged 36 years, who died after copious hæmatemesis, having for nearly six years had jaundice. The liver seems to have diminished, as possibly it did likewise in Case No. 2, during the latter part of the disease. The xanthoma which was present is stated to have disappeared before the patient's death. The *necropsy* showed general matting together of all the abdominal contents by old peritonitis and obstruction to the passage of bile by an egg-shaped gall-stone weighing 4 grammes when dry. The spleen weighed 21 oz., but is supposed to have been still larger before the final hæmatemesis. The liver was much cirrhosed, had a granular surface, as Dr. Chadwick informed me, and was of a decidedly green colour. Through Dr. Chadwick's kindness I had the oppor-

[1] 'Brit. Med. Journ.,' 1895, vol. i, p. 1143.

tunity of examining sections of the liver; they resembled the preparations from No. 1 and No. 2.

CASE 4.—Dr. Humbert Mollière's case[1] was doubtless another example of the same kind, only that in his patient, a woman aged 70 years, with jaundice of over two years' duration, a large calculus seems to have *completely* blocked the lower part of the common bile-duct. The liver was hard, enlarged, and of a greenish colour. The bile-ducts were hypertrophied and dilated, and contained a blackish powdery material.

CASE 5.—S. J. Sharkey[2] describes the case of a young man aged 20 years, with jaundice and biliary cirrhosis, who died after an operation. There were gall-stones in the gall-bladder, but none were found in the common bile-duct. Dr. Sharkey thinks the cirrhosis in this case was an example of Hanot's disease, and not due to cholelithiasis. It must be noted, however, that the examination after death was limited to what could be discovered through the laparotomy wound. The patient's mother had apparently at one time suffered from cholelithiasis.

CASE 6.—The case of Gilbert and Fournier.[3] A woman of healthy antecedents, at the age of 25 years commenced to suffer from recurrent attacks of biliary colic with fever. Jaundice, sometimes more, sometimes less, persisted from the time of the second attack until her death. On examination three years after the commencement of the illness, there was deep jaundice, pruritus, and xanthoma. The liver was enlarged and hard, its surface was smooth, and it was tender to palpation. The lower edge of the spleen could be felt five finger-breadths below the costal margin. No ascites. There was diarrhœa, and the fæces were sometimes coloured, sometimes not, according to the degree of the jaundice. Appetite good. Puncture of the liver enabled the presence of *B. coli* to be recognised in that organ. No gall-stones were detected by an exploratory operation. The general condition improved, but three months later the patient suffered

[1] 'Lyon Médical,' vol. xviii, p. 198.

[2] 'St. Thomas's Hospital Reports,' New Series, vol. xviii, p. 245.

[3] 'Comptes Rendus de la Soc. de Biologie,' Paris, July 10th, 1897, p. 692. Quoted by Lereboullet, loc. cit.

from hæmatemesis, epistaxis, hæmaturia, and hyperpyrexia, and she sank rapidly. At the *necropsy* the extra-hepatic bile-ducts were a little dilated, and a calculus was found in the choledochus which did not completely obstruct the channel. The hepatic cirrhosis was of somewhat irregular multilobular distribution. There were no newly formed biliary canaliculi, and a good many of the original canaliculi had apparently been obliterated.

CASE 7.—The following case was described by T. Legry:[1]—The patient, a woman aged 57 years, in the clinic of Professor Cornil, at Paris, had had jaundice for twenty years. There was no evidence of alcoholism. The jaundice commenced after her sixth pregnancy, and its onset was accompanied by pains, not very severe, in the right hypochondriac and epigastric regions. Some months later on the pains were worse, but were never accompanied by vomiting. In spite of the chronic jaundice her general condition had remained fairly good until a year before admission to the hospital, when she became weaker. Six months before admission her legs and belly began to swell. On admission there was ascites. The fæces were normally coloured. The urine was free from albumen and sugar. After paracentesis and removal of nine litres of ascitic fluid, the liver could be felt hard, evenly enlarged, and reaching two inches below the costal margin. The loss of strength increased rapidly, and the patient died about two weeks after admission. At the *necropsy* the heart was found flabby, and seemed to have undergone a certain amount of fatty degeneration. There was hypostatic congestion of the lungs, and ecchymoses of the mucous membranes of the stomach, duodenum, and uterus, and of the pelvis of the kidneys. The spleen was enlarged, measuring $8 \times 4\frac{1}{4} \times 2\frac{3}{8}$ inches, and there was some perisplenitis. The liver was enlarged, cirrhosed, and its surface granular. On cutting into the organ the intra-hepatic bile-ducts were seen to be dilated, and some of them were blocked by concretions. The common bile-duct contained calculi, which probably did not completely obstruct it. The gall-bladder was somewhat contracted. There were enlarged lymphatic glands

[1] 'Bulletins de la Société Anatomique,' Paris, May 31st, 1899, p. 405. Quoted by Lereboullet, loc. cit.

at the hilum of the liver, and elsewhere in the abdomen and thorax. Microscopic examination of the liver showed great fibrosis, the distribution of the fibroid tissue being in the main unilobular.

CASE 8.—E. Tison's case.[1] The patient was a woman aged 39 years. Her illness had commenced with hepatic colic and jaundice five years previously. The jaundice had persisted from that time. She had had occasional attacks of hepatic pain, but had been able to continue her work to within a year of her death. Seven months before death she had severe attacks of hepatic pain, hæmatemesis, and melæna. The jaundice deepened. On admission to the hospital she was feeble and emaciated and intensely jaundiced. Xanthoma was noted at the inner angles of the eyelids. There was œdema of the lower extremities and slight ascites. The subcutaneous veins of the abdomen were not dilated. The liver was felt hard, and reached about five finger-breadths below the costal margin. The spleen was enlarged and tender to pressure. The fæces were yellowish, never quite devoid of colour. The bilious urine contained no albumen. The patient was feverish and dyspnœic, and died four days after admission. At the *necropsy* the liver (weight 67½ oz.) was enlarged and hard; its surface was uneven and greyish, but the colour on cutting into it was yellowish green. The common bile-duct, the hepatic duct, and the gall-bladder were dilated and full of calculi. Some of the intra-hepatic bile-ducts contained biliary sand and calculi. The spleen was enlarged and soft. The lymphatic glands at the hilum of the liver were enlarged and pigmented. The heart was flabby, and the lungs were emphysematous with hypostatic congestion. Microscopic examination of the liver showed that the cirrhosis was irregular in distribution. Some of the hepatic cells took on the stain badly. Tison thought there were no newly formed biliary canaliculi.

CASE 9.—Rabé's case.[2] The patient was a man aged 73 years, who died with the symptoms of atrophic cirrhosis. He

[1] 'Bulletins de la Société Anatomique,' Paris, November, 1888, p. 969. Quoted by Lereboullet, loc. cit.

[2] Ibid., February, 1898, p. 170.

never had jaundice. There was ascites. Evidence of chronic alcoholism was forthcoming. At the *necropsy* a calculus was found in the ampulla of Vater, and there was pylephlebitis obliterans. The distribution of the hepatic cirrhosis was chiefly multilobular, but to a lesser degree also unilobular. The man seems therefore to have had ordinary cirrhosis connected with his alcoholism, and a certain amount of biliary cirrhosis connected with his cholelithiasis.

CASE 10.—A. Krokiewicz's case.[1] The patient was a man aged 57 years, with jaundice, large liver, and large spleen. The illness was supposed to be of one year's duration. He died about five weeks after admission to the hospital. The *necropsy* showed dilatation of the common, hepatic, and cystic bile-ducts, and the presence of gall-stones in the gall-bladder. The orifice of the common bile-duct was stenosed by incipient carcinoma. The liver was enlarged, hard, and its parenchyma was of a greenish-brown colour. Microscopically the distribution of the cirrhosis was irregular. This case can only be included here on the supposition that cholelithiasis preceded the carcinomatous stenosis of the common bile-duct.

CASE 11.—A case described by W. W. Ford.[2] The patient was a woman aged 28 years, with jaundice of three years' duration. She had ascites and œdema of the lower extremities, and the superficial abdominal veins were dilated. Coma and death occurred about a month after admission to the hospital. At the *necropsy* the liver was found greatly enlarged, of tough consistence, and with granular surface; by microscopic examination it is said to have shown interlobular and intra-lobular cirrhosis, with increase of biliary canaliculi. The hepatic duct was slightly dilated, and contained a loose calculus pressing on the cystic duct at its orifice; the cystic duct was obliterated and the gall-bladder thickened.

CASE 12.—A case also described by Dr. Ford.[3] The patient was a man aged 53 years, admitted to the hospital with jaundice, pruritus, and enlarged liver. His symptoms (attacks

[1] 'Wiener klin. Wochenschrift,' 1898, No. 13, p. 320.
[2] Loc. cit., p. 68.
[3] Loc. cit., p. 70.

of epigastric pain and vomiting) were of over two years' duration. He died from hæmorrhage after the operation of cholecystoduodenostomy, shortly after admission. No calculus was found at the operation or at the *necropsy*, but some ulceration near the orifice of the common bile-duct pointed to the recent passage of a calculus. The common, hepatic, and cystic bile-ducts were greatly dilated. Microscopic examination of the liver, which was enlarged, firm, and granular, showed an early stage of interlobular cirrhosis, with dilatation of the biliary ducts and deposit of bile pigment in many of the hepatic cells.

Cases of jaundice of two to seven years' duration, or still more chronic, are to be found scattered about in the literature of the subject. Many of these almost certainly belong to the class of chronic cholelithiasis with biliary cirrhosis, and yet will not serve as illustrations, either because no *post-mortem* examination was recorded,[1] or because the description of the liver was omitted, or because fatal ulceration or fatal suppurative cholangitis supervened and obscured the original pathological anatomical features. Doubtless many other cases have remained unpublished; to one interesting unpublished case I shall afterwards (by permission) allude.

Changes found in biliary cirrhosis with cholelithiasis.—The cases of which I have given abstracts serve to illustrate the anatomical changes in biliary cirrhosis with cholelithiasis. The enlargement of the liver is fairly uniform, and though the surface of the organ may present a granular or slightly puckered appearance from contraction of the newly formed

[1] For instance, the case reported by W. T. Mills ('Brit. Med. Journ.,' July 6th, 1901), in which a patient known to have passed gall-stones developed a large, hard liver without ascites, and died about four and a half years after the attack of cholelithiasis. One cannot help thinking that certain very chronic cases of jaundice and cholelithiasis must have had likewise some degree of biliary cirrhosis, although recovery from the jaundice was recorded. For instance, there is Van Swieten's case of a woman, sixty years of age, who had jaundice for twelve years, firstly at intervals, but during the last year continuously; she got rid of her jaundice after much discharge of sandy material with the fæces ('Commentaries of Van Swieten,' English translation, 1765, vol. ix, p. 270). Then there is Murchison's case of a woman, about forty years old, who recovered from her symptoms after more or less persistent jaundice from gall-stones during nearly six years (Murchison's 'Clinical Lectures on Diseases of the Liver,' third edition, p. 417).

connective tissue, and may have a few projecting nodules (possibly representing an attempt at compensatory hyperplasia[1] of the glandular tissue), it has little or none of the coarse "hob-nail" irregularity often seen in ordinary cirrhosis. The liver is generally, but not always, much enlarged, and its colour is greenish, owing probably to the long duration of the jaundice. The distribution of the newly formed connective tissue, excepting perhaps at a few spots here and there, is not strictly "unilobular." All that can be said is that it is more uniform and more inclined to be unilobular than in cases of ordinary cirrhosis. This finer distribution in the cirrhotic process is better seen by naked-eye examination of a freshly cut surface than by studying microscopic preparations. The hepatic parenchyma apparently contains less fat than that from a case of ordinary cirrhosis. I have seen nothing to make me believe that any changes occur in the bile-ducts analogous to xanthoma of the skin.[2] The associated enlargement of the spleen is generally greater than in cases of ordinary cirrhosis.

The cause of the cirrhosis.—I now believe that the cause of the cirrhosis in these cases is twofold—partly an obstruction to the outflow of bile from the liver, and partly a chronic inflammation of the bile-ducts.

The experimental evidence in favour of obstruction to the bile flow as a possible cause of cirrhosis is very strong. Besides the English work on this subject already men-

[1] In cirrhotic livers it is probably not always possible to sharply distinguish between multiple adenomata (that is, *hyperplasia-like tumour-formation*) and nodular compensatory overgrowth of the parenchyma, as seen in ordinary hob-nail livers (that is, *tumour-like hyperplasia*). In either case malignant tumour-formation may supervene. The increase of bile canaliculi, when present, must likewise in part be regarded as representing a process of tumour-like hyperplasia or hyperplasia-like tumour-formation.

[2] The existence of a xanthomatous swelling of the walls of the biliary ducts, as the cause of an obstructive jaundice and of hypertrophic cirrhosis of the liver, is unlikely. There is evidence that all forms of xanthoma eruption (except perhaps the slight "hereditary" or "family" cases) are associated with functional or organic disorders of the liver and abdominal viscera, whether jaundice be present or not. Even the rare form "xanthoma diabeticorum" has usually occurred, not in the severest cases of diabetes, but in stout persons, with only slight or occasional glycosuria, in whom some more or less chronic derangement of the abdominal viscera (liver or pancreas or both) is probable. Compare Mr. J. Hutchinson's remarks on "Xanthelasma and Xanthoma" in the New Sydenham Society's 'Atlas of Illustrations,' fasc. xv, 1902.

tioned, I need only refer to the well-known investigations of H. Mayer[1] (1872), Charcot and Gombault[2] (1876), D. Gerhardt[3] (1892), and D. Nasse[4] (1894). It is quite true, as may be objected, that the existence of cholelithiasis almost implies the existence of a disordered condition of the biliary passages,[5] but one cannot infer from this that the cases of biliary cirrhosis following cholelithiasis are due merely to the same disorder of the bile-ducts which led to the formation of the gall-stones. If they were, one would expect biliary cirrhosis to occur more frequently with gall-stones in the gall-bladder or cystic duct, whereas in the cholelithiasis cases in which cirrhosis has developed the gall-stones have been located in the common or hepatic bile-duct. Moreover, obstruction to the outflow of bile from causes other than gall-stones[6] suffices, if very chronic, to induce cirrhotic changes in the human subject, as it does experimentally in animals.

In regard to the way in which obstruction to the bile flow induces cirrhosis, I shall quote Vaughan Harley and Barratt,[7] who, from experimental ligature of a single bile-duct in animals, considered the most probable explanation to be as follows:

(1) The interlobular fibrosis is attributable to the continued slight irritation set up by bile which passes through the walls of the smaller bile-ducts by osmosis, caused by the increased

[1] 'Medicinische Jahrbücher,' Vienna, 1872, p. 133.

[2] 'Archives de Physiologie,' 1876, second series, vol. iii, p. 272.

[3] 'Arch. für exp. Pathologie und Pharm.,' 1892, vol. xxx, p. 1.

[4] 'Arch. für klin. Chirurgie,' 1894, vol. xlviii, p. 885.

[5] Naunyn ('Verhandlungen des X Congresses f. inn. Medicin,' 1891, p. 25) believed that a morbid condition of the mucous membrane formed a necessary antecedent to the formation of calculi in the gall-bladder. This conclusion has been confirmed by the experiments of J. Mayer ('Virchow's Arch.,' 1894, vol. cxxxvi, p. 561), Mignot (Société Anatomique, Paris, June 24th, 1898, and 'Arch. gén. de Méd.,' August, 1898), F. E. Italia ('Policlinico,' March, 1901, vol. viii, p. 153), and others, regarding the *rôle* of microbes (*B. coli* and other microbes if their virulence is not sufficient to cause suppuration) in the etiology of cholelithiasis. Dr. Italia gives a good bibliography of the subject.

[6] Cf. W. W. Ford's paper on "Obstructive Biliary Cirrhosis," loc. cit. Amongst other cases he quotes Benner's (1899), in which the obstruction was due to a primary adeno-carcinoma of the common bile-duct. Obstruction in large ducts is doubtless *one of the causes* of the biliary cirrhosis in cases of so-called "congenital obliteration of bile-ducts;" but to this subject I shall refer later on.

[7] Loc. cit.

pressure of the bile resulting from ligature. Rupture of the smaller bile-ducts probably is not an effective factor in experimentally induced cirrhosis. (2) The dilatation of the larger bile-ducts and the marked increase of the smaller ones is, in part at any rate, directly due to the ligature, and is comparable to the extreme elongation and increase in size of the veins and venules which is seen in considerable degrees of varix of the lower extremities and in varicocele. Our observations have so far failed to afford proof of other modes of formation of the interlobular bile-ducts.[1] (3) The atrophy of the lobules is due chiefly to the irritant effects of bile which has passed out of the bile-ducts, and which acts principally, if not almost exclusively, upon the peripheral portion of the lobule. It does not appear that pressure upon the lobules caused by the newly-formed interlobular fibrous tissue is an effective factor in causing atrophy.

In neither of my own cases (Cases No. 1 and No. 2) of biliary cirrhosis with cholelithiasis was increase of bile canaliculi obvious on microscopic examination of sections of the liver. In neither of these cases in the latter part of the disease was there persistent complete obstruction to the escape of bile by the common duct, although a small calculus lying loose in the dilated ducts may have occasionally completely occluded the orifice into the duodenum by a kind of ball-valve action. The analogy, therefore, between experimental occlusion of bile-ducts by ligature and obstruction by gall-stones is not perfect, for the experimental blocking is complete, whilst the gall-stone obstruction may be intermittent or incomplete, as it was in my two cases.

Of chronic cholangitis as a causative factor in biliary cirrhosis of the liver, I shall have to say more presently.

On the whole, in regard to its pathogeny, biliary cirrhosis,

[1] The microscopic appearances in human cases of cirrhosis point, I think, to the canaliculi being partly original and partly newly formed by transformation of hepatic cells. D. Gerhardt's illustrations (loc. cit.) from his experimental cases point to there being a formation of new bile canaliculi by atrophy of liver-cells. I think the increase in canaliculi must partly likewise in human cases be regarded as representing a process of *tumour-like hyperplasia* or *hyperplasia-like tumour formation*, analogous to nodular compensatory overgrowth of the liver-cells or to multiple adenomata in cirrhotic livers (cf. previous foot-note on the subject).

when it is associated with cholelithiasis and dilatation of the large bile-ducts, may, I think, fitly be compared to the chronic interstitial nephritis which accompanies dilatation of the urinary passages from long-continued partial or intermittent obstruction to the outflow of urine. In both cases, moreover, an acute suppurative ascending inflammation may supervene as the final cause of death. To say that because bile passes into the duodenum chronic obstruction in the common bile-duct cannot be a cause of the hepatic cirrhosis, is like saying that because a man with urethral stricture or enlarged prostate has been able to pass urine, obstruction in the urethra cannot have been the cause of his dilated ureters and chronic interstitial nephritis.[1]

I must add that a case was kindly brought to my notice by my colleague, Dr. Zum Busch (in 1898), in which a condition of obstructive cholelithiasis was found associated with jaundice of nine or ten years' duration. In spite of the long duration of the jaundice the liver had undergone decidedly less cirrhotic change than in my own cases. This may be explained either as due to relative difference in tissue proclivities, or by supposing that chronic jaundice with chronic cholangitis, but without hepatic cirrhosis, may precede the cholelithiasis and cirrhosis.

In regard to the latter supposition, Dr. Sharkey's case (No. 6) may, as he suggests, have been a case of Hanot's disease with cholelithiasis as a mere complication. Biliary cirrhosis, as we shall later point out, results from cholangitic changes, just as, to some extent, cholelithiasis does. In fact, in Sharkey's and some other cases the biliary cirrhosis and the cholelithiasis may both equally have owed their origin to a chronic cholangitis.

In regard to the former supposition, I believe that there is such a thing as a predisposition of the hepatic tissue (special tissue proclivity) to cirrhotic change, and that a certain amount of obstruction to the bile flow and of chronic cholangitis may fail to produce cirrhosis in some persons, which in others (more predisposed) is amply sufficient. Probably, however, the persistent presence of a calculus in the common bile-duct, with the chronic cholangitis and intestinal and

[1] May not the occasional association of pancreatic lithiasis with a fibrotic change in the whole pancreas be explained in the same way as biliary cirrhosis of the liver in cases of obstructive cholelithiasis?

metabolic disturbance necessarily accompanying it, is sufficient in all cases ultimately to set up a condition of biliary cirrhosis.

Part II.—Biliary Cirrhosis without Gall-stones and without Obstruction in the Common Bile-duct.[1]

The characters of the liver in these cases are very similar to those described in the preceding section. The surface of the organ has seldom a typical coarse "hobnail" appearance, but may be granular, or at all events not quite smooth. The cirrhotic process is generally fairly uniform, but is seldom or never strictly unilobular, as it has sometimes been supposed to be, excepting at spots here and there. There is generally increase of bile canaliculi, and granules of inspissated bile pigment are seen in the small bile-ducts and liver-cells.

The disease is mainly one of childhood and the period of growth, but may commence in later years (as in Hanot's original cases). Sometimes more than one case may occur in the same family. When it commences early the disease may lead to stunting of the child's growth, a partial arrest of development, or infantilism. It is generally associated with a tendency to bleeding from the nose, gums, etc., but these "cholæmic" hæmorrhages are never accompanied by the peculiar articular swellings of hæmophilia. The typical form of the disease is a "hypertrophic cirrhosis with chronic jaundice" (the real "Hanot's disease," according to Hanot's original publications), but the degree of jaundice differs much in different cases, and may vary considerably in the same case from time to time (exacerbations and remissions of the disease). In some cases apparently jaundice may be absent for a long period at the commencement of the disease. The liver is nearly always much enlarged, but, as in other forms of cirrhosis, atrophic changes may occur, and at the *post-mortem* examination the organ may be found not much, if at all, increased in size and weight. The spleen is generally much enlarged, and in some cases may be excessively big early in the disease; the splenic tumour may form one of the most striking clinical features of

[1] In the present paper I shall not specially consider the cases in which a certain amount of biliary cirrhosis occurs owing to obstruction of the common or hepatic bile-duct from causes (tumours, etc.) other than gall-stones.

the case. A varying amount of pigmentation of the skin, other than icteric, is usually present, as in most cases of chronic jaundice, but in some cases this pigmentation is very striking, and may even bring the question of Addison's disease to mind. Alcohol, syphilis, and malaria play no essential parts in the etiology of the disease.

Cases of the disease have been described by Hanot,[1] Schachmann,[2] Gilbert and Fournier,[3] Gilbert and Castaigne,[4] Gilbert and Lereboullet;[5] and, in Great Britain, by F. Taylor,[6] H. R. Smith,[7] J. Finlayson,[8] A. W. Fox,[9] F. J. Smith.[10] Many more references are given in the recent work on biliary cirrhosis by Lereboullet,[11] in which he has contributed descriptions of several fresh cases. I shall here content myself with giving a short description of a case which I had the opportunity of observing, and which illustrates several important points connected with the disease.

The case[12] was that of a girl, J. S—, aged 14 years, who was under my care at the German Hospital, where she died in February, 1895. She had, her father thought, been more or less jaundiced all her life, and had always been weakly and thin, though she had never had any serious acute illness. She had, I think, repeatedly had bleeding from the nose and gums. She was extremely ill-developed for her age, and looked very much younger than she really was. Her skin was jaundiced, and likewise much darkened from chronic pigmentation; there were two or three capillary "stigmata." The liver could be felt consider-

[1] "Étude sur une forme de Cirrhose hypertrophique du Foie avec Ictère chronique," 'Thèse de Paris,' 1875; and 'Bulletin médical,' Paris, September 27th, 1893. Cf. Hanot and Schachmann's conjoint study in 'Archives de Physiologie,' Paris, 1887, vol. ix, p. 1.

[2] "Cirrhose hypertrophique avec Ictère chronique," 'Thèse de Paris,' 1887.

[3] 'Revue mensuelle des Maladies de l'Enfance,' 1895, vol. xiii, p. 310.

[4] Soc. de Biologie, 1899 and 1900 (various papers).

[5] 'Gazette hebdom.,' Paris, April 19th, 1900, p. 361. This case, like many others, is included by Lereboullet, loc. cit.

[6] 'Guy's Hospital Reports,' vols. lii and liv.

[7] 'Trans. Clinical Soc. of London,' 1898, vol. xxxi, p. 258.

[8] 'Glasgow Hosp. Reports,' 1899, vol. ii, p. 39.

[9] 'Brit. Med. Journ.,' 1878, vol. ii, p. 913. Typical Hanot's disease in a boy aged 11 years whose mother was a drinker.

[10] 'Trans. Path. Soc. London,' 1890, vol. xli, p. 154.

[11] Op. cit.

[12] F. P. Weber, 'Trans. Path. Soc. London,' 1895, vol. xlvi, p. 71.

ably below the costal margin, but the spleen was excessively large, reaching to below the anterior superior iliac spine. There was irregular fever, and, during the last weeks, ascites. One sister was said to have become jaundiced at about the age of 13 years, and to have died at 19 years with symptoms somewhat resembling those of J. S—. At the *necropsy* on the latter the liver was green, hard, and "hobnailed." Perhaps I ought to have described it as having an irregular, scarcely amounting to "hobnail" surface. It only weighed 26½ oz. Microscopic examination of the sections showed a large amount of fibroid tissue, dividing the glandular substance into unequal compartments, and sometimes invading the lobules, entering between

FIG. 11.

Showing the microscopic appearances in the liver of J. S—. (× 50.)

the individual hepatic cells. There was a good deal of small-cell infiltration in the scar tissue. There was not very great increase of bile canaliculi, but much green inspissated bile could be seen situated between or in the hepatic cells, which on the whole contained relatively little fat. The gall-bladder contained a moderate amount of clear, almost colourless fluid. The common bile-duct was unfortunately not examined. There was no perihepatitis. The spleen, uniformly enlarged, weighed 20½ oz.; on section its substance seemed rather firm, but otherwise normal; the microscope showed increase in fibrous tissue, and considerable deposit of pigment in some of the trabeculæ.

The lymph-glands, especially those at the hilum of the liver, were somewhat enlarged and much pigmented.

Amongst the points in regard to Hanot's disease which this case illustrates, are the following:—(1) In some cases of long duration the cirrhosis may be said to become almost "atrophic," instead of "hypertrophic," whilst the contraction of the newly formed fibroid tissue and the nodules representing an attempt at compensatory hyperplasia of the gland-cells, may give the surface of the liver an almost "hobnail" appearance, as in ordinary cirrhosis. (2) The fibrosis, though more regular than in many cases of ordinary cirrhosis, is not purely "unilobular" in distribution. (3) The growth of the patient's whole body may be stunted when the disease commences in early childhood. (4) The enlargement of the spleen, especially in children, may be so great as to constitute the most striking clinical feature of the case. (5) The case further illustrates the occasional tendency to Hanot's disease in different members of the same family. It is worth mentioning that the child's mother was a drinker, just as the mother in Dr. A. W. Fox's case was.[1]

Amongst the occasional features of the disease, which my case did not illustrate, are the clubbing of the fingers and various trophic disorders of the extremities which have been sometimes noted in patients with biliary cirrhosis and other forms of chronic hepatic disease.[2]

Pathogeny.—In the cases of biliary cirrhosis without, as in the cases with, cholelithiasis, I believe the cirrhosis is due to (1) chronic or subacute cholangitis, and possibly temporary attacks of acute cholangitis or acute exacerbations of chronic cholangitis;[3] (2) obstruction to the outflow of bile. In these cases, however, the obstruction must be in the minute bile-ducts, and is probably due to the cholangitis. This affords an explanation for the remissions

[1] Loc. cit.

[2] *Vide* Gilbert and Lereboullet, "Le Doigt Hippocratique dans les Cirrhoses biliaires," 'Gazette hebdom.,' January 2nd, 1902. These authors think that a toxæmia from the cholangitic disease plays a great part in the production of the clubbed fingers and of an arthropathy which they term "biliary rheumatism," but they also think that there is an "individual element" of importance in these cases, not every one being equally liable to get clubbed fingers from the same cause.

[3] Many French authors insist on an infection of the gall-ducts as the main etiological factor both in biliary cirrhosis and in chronic "simple jaundice" without cirrhosis. *Vide* Lereboullet, op. cit.

and exacerbations of the jaundice and other symptoms in the disease. If there is a condition of chronic cholangitis of the large and medium-sized ducts, one can understand that a few of the smaller ducts may be likewise more or less constantly affected, and, owing to some of the minute channels being always blocked, the persistence of a certain degree of permanent jaundice becomes intelligible. During exacerbation of the cholangitis a larger number of the minute bile-ducts will become blocked, and a temporary increase of the jaundice and other symptoms will be the natural result. This process may be compared to what takes place in chronic bronchitis. A certain amount of bronchial catarrh may exist without giving rise to much trouble, and urgent symptoms may only occur during exacerbations of the disease, when many of the small bronchial tubes become affected as well as the large ones. I do not mean to say that either the cholangitis or the bronchitis must necessarily be solely due to the local presence of microbes. One can quite well imagine that an irritation of excretory origin may cause the inflammation and the exacerbations of inflammation in either disease. In some subjects dietetic or metabolic disturbances almost certainly give rise to attacks of bronchitis or exacerbations of chronic bronchitis, and in such persons the bronchitis may be due to irritation of the epithelium from the altered quality of blood and the resulting abnormality in the bronchial secretion.

Rolleston, who has specially insisted on the probable excretory origin of the cholangitis, suggests that the latter may be due to a poison reaching the small bile-ducts by the blood, as in experimental poisoning by toluylendiamine. He aptly terms the disease commencing in the biliary radicles a "descending cholangitis," and thus distinguishes it from "ascending cholangitis"—that is, an inflammation of the bile-ducts spreading upwards from the duodenum. If this supposition of an excretory and descending cholangitis be correct, as it probably is for some cases, the cholangitis and pericholangitis, which give rise to the cirrhotic changes spreading from the small bile-ducts, may be compared to the inflammation of and around the capsules of Bowman in scarlatinal nephritis (likewise doubtless an "excretory inflammation"); the resulting biliary cirrhosis may be further compared to chronic interstitial nephritis following

scarlatina.[1] In both cases, moreover, one must suppose that the resulting cicatricial changes need not necessarily be progressive in character; certain clinical phenomena are thus explained (see later in regard to the occurrence of chronic jaundice without obvious changes in liver or spleen).

Be this as it may, there can scarcely be a doubt that unwholesome substances taken in food or drink, or for some special purpose, and auto-intoxication due to abnormal conditions of the digestive organs, may be factors in the production of biliary cirrhosis, as in that of ordinary cirrhosis. It seems to me, moreover, that the question of drugs being excreted by the liver suggests the possibility of further useful drug-treatment being discovered for cases of cholangitis and biliary cirrhosis. Some drug may be discovered which, during the process of its elimination from the body, exercises as salutary an effect on abnormal conditions of the bile-ducts as chlorate of potash when taken internally does on certain abnormal conditions of the mouth and fauces; the action of urotropin in certain disorders of the urinary passages may likewise be borne in mind.

Family tendency to biliary cirrhosis (Hanot's disease).

A sister of J. S—, the patient[2] to whom I have already alluded, was likewise affected. J. Dreschfeld[3] met with the disease in two brothers, one of whom was a drinker and the other temperate. Osler[4] mentions two brothers affected with the disease. Boinet[5] wrote of a family in which the father and two children had biliary cirrhosis, and three other children had enlarged spleens. J. Finlayson[6] speaks of three brothers and a sister, two of whom had biliary cirrhosis, one had enlargement of the liver and spleen with icterus, and one had slight jaundice.

[1] This comparison further illustrates how in a glandular organ, such as the liver or kidney, inflammation around the minute blood-vessels and inflammation around the duct-radicles are likely to accompany each other as indistinguishable parts of a common process.

[2] 'Trans. Path. Soc.,' 1895, loc. cit.

[3] 'Medical Chronicle,' April, 1896, p. 19. Quoted by Rolleston, 'Encyc. Med.,' loc. cit.

[4] 'Principles and Practice of Medicine,' fourth edition, p. 574.

[5] 'Arch. gén. de Méd.,' April, 1898, p. 385. Quoted by Rolleston, loc. cit.

[6] 'Glasgow Hospital Reports,' 1899, vol. ii, p. 39.

Hasenclever[1] has recorded an instance of three members of one family, a boy and two of his sisters, having typical biliary cirrhosis. There is therefore no doubt whatever that a family tendency to biliary cirrhosis is occasionally met with.[2] In the same way a special proclivity to ordinary attacks of catarrhal jaundice occurs in some families,[3] and in others there is a special tendency to cholelithiasis.

If one admits the existence of a diathesis which consists in a tendency to non-suppurative cholangitis (whether descending or ascending, and whether due to the local presence of microbes or not), and if one admits that this diathesis may run in families, the mutual relation of tendencies to simple attacks of catarrhal jaundice, to the more chronic "simple cholæmia" (with or without actual jaundice) of French authors, to cholelithiasis, and to biliary cirrhosis, becomes evident, and an explanation is afforded for the occasional occurrence of these different types of biliary disease in different members of the same family.[4]

The enlargement of the spleen in biliary cirrhosis.

Various explanations have been offered for the association of enlargement of the spleen with hepatic cirrhosis. Formerly

[1] 'Berl. klin. Woch.,' 1898, No. 45, p. 997.

[2] In Hindoo families about Calcutta a cirrhosis, which from histological examination was supposed by Paltauf and Kundrat, of Vienna, to be a form of biliary cirrhosis, is common among infants, and has been noted to attack several children in the same family (cf. Gibbons, "The Morbid Anatomy and Pathology of the Form of Biliary Cirrhosis which occurs in Children in India," read at the Indian Medical Congress, Calcutta, 1894; also Manson, 'Tropical Diseases,' 1898, p. 379). There have perhaps also been instances of the ordinary type of hepatic cirrhosis occurring in different members of the same family, and apart from any influence of alcohol. F. W. Jollye ('Brit. Med. Journ.,' April 23rd, 1892, p. 858) speaks of a brother and sister being affected by hepatic cirrhosis, which seems to have been of the ordinary type; and though there was no history of alcohol, both the children had indulged inordinately in vinegar. R. P. Howard ('Amer. Journ. Med. Sci.,' October, 1887, p. 350) gives the case of a girl aged nine years dying of what seems to have been a biliary type of cirrhosis, whose brother died six years later, when about ten years old, of what seems to have been the ordinary type of cirrhosis.

[3] H. Benedict ('Deut. med. Woch.,' April 17th, 1902) describes what seems to be a variety of this fairly common "family disposition" to jaundice—namely, a special liability, affecting two sisters, to suffer from jaundice during pregnancy.

[4] Cf. Lereboullet, loc. cit.

the enlargement of the spleen was generally believed to be the result of congestion from obstruction in the liver to the portal circulation. R. Oestreich[1] pointed out that, in most cases, the enlarged spleen was soft, quite different from the hard spleen of passive congestion from heart disease. He considered the enlargement as mainly due to a hyperplasia of the splenic pulp, which he ascribed to irritation. Ziegler[2] says that, though the splenic enlargement is usually regarded as due to chronic venous engorgement, the pulp is fairly soft and not so dark red as in the spleen of simple passive congestion. In a previous study[3] I came to the conclusion that an auto-intoxication, caused by the hepatic disease, is probably the chief cause of the splenic enlargement. In biliary cirrhosis the enlargement of the spleen is generally more marked than in ordinary cirrhosis, and it is generally relatively greater in children than in adults. Gilbert and Lereboullet[4] think that the enlargement is due partly to passive congestion and partly to a direct infection from the liver by the blood, favoured by temporary stagnation of the blood in the splenic vein. It has been suggested that both the liver disease and the splenic enlargement are due to the same cause—namely, a condition of toxæmia from abnormal absorption from the alimentary canal.

In splenic anæmia (including Banti's disease) it has been urged that the splenic disease causes the hepatic cirrhosis (which sometimes supervenes at a later stage of the disease) by setting up a condition of toxæmia. There is, however, no reason for believing that, in the cases of biliary cirrhosis which we are now considering, the splenic condition is the cause of the cirrhosis. Even when enlargement of the spleen precedes the physical signs of the hepatic cirrhosis, it seems more probable that a condition of cholangitis, preceding the cirrhosis, gives rise, after the manner of an infectious disease, to the splenic enlargement. Many cases of chronic, sometimes congenital, jaundice with enlarged spleen, but apparently without cirrhosis of the liver, have been described under the heading

[1] 'Virchow's Arch.,' 1895, vol. cxlii.

[2] 'Special Pathological Anatomy,' English edition by McAlister and Cattell, from eighth German edition, p. 114.

[3] "The Cause of Splenic Enlargement in Cases of Hepatic Cirrhosis," 'Edinburgh Medical Journal,' December, 1897.

[4] 'Comptes Rendus de la Soc. de Biologie,' Paris, March 30th, 1901, p. 375.

"Ictère chronique splénomégalique," by Lereboullet[1] and others.

It must be remembered that in certain individuals, particularly in children, a chronic enlargement of the spleen may be caused by a temporary feverish or toxæmic condition, which would not be sufficient to cause splenic enlargement in most persons. A tendency to enlargement of the spleen, and sometimes of the lymphatic tissues in general, from slight causes may occur in several members of a family. Such a special "tissue proclivity" might account for there being certain families in which several members have chronic enlargement of the spleen and suffer from persistent slight jaundice or occasional attacks of jaundice.[2] It has been suggested that the affected members of these families are examples of splenic anæmia (Banti's disease), and that the hepatic symptoms are secondary to the splenic disease. Strongly against this view is what I believe to be a fact, namely, that in none of these cases has undoubted splenic anæmia been known to supervene, whereas the slight enlargement of the liver noted in some of the cases, and the attacks of jaundice and fever, suggest the existence of recurrent exacerbations of cholangitis threatening to set up actual biliary cirrhosis.

[1] Loc. cit.

[2] A family series of such cases was described by Dr. Claude Wilson ('Trans. Clin. Soc. London,' vol. xxiii, p. 162, and vol. xxvi, p. 163). A family series of similar cases is published by Dr. J. A. Arkwright ('Edinburgh Medical Journal,' January, 1903, p. 52), consisting of father, one son, and one daughter, in a non-malarial country, with considerably enlarged and hardened spleens, persistent slight jaundice, and occasional attacks of fever, vomiting, and temporary increase of the jaundice. In both a mother and her son, shown by Sir Thomas Barlow and Dr. H. Batty Shaw at the Clinical Society of London (May 23rd, 1902), there was splenic enlargement and a slight degree of persistent jaundice, but the mother, owing to the enlargement of the liver, probably had actual biliary cirrhosis. Amongst the cases of "ictère chronique splénomégalique" described by Lereboullet (loc. cit., pp. 447—464) there are some family groups comparable to these. As illustrating the possible toxic or "hæmo-hepatogenous" origin of exacerbations of jaundice in some cases of "ictère chronique splénomégalique," a paper by Bettmann in the 'Münchener medicinische Wochenschrift' (June 5th, 1900, p. 791) may be referred to. He describes the case of a merchant, aged 29 years, with a large spleen, and moderate jaundice from early childhood; there are occasional exacerbations of symptoms, and there has been at least one attack of paroxysmal hæmoglobinuria, the latter proving the occurrence of excessive hæmatolysis.

From what I have said, it is evident that I am against any classification of biliary cirrhosis according to the relative size of the spleen in different cases. Thus I would not adopt the French division into cases of cirrhose biliaire "splénomégalique" or "hypersplénomégalique," and cirrhose biliaire "microsplénique" or "asplénomégalique," though there have been exceptional cases of biliary cirrhosis without splenic enlargement.[1]

Congenital biliary cirrhosis, and the relation of biliary cirrhosis to congenital abnormalities of the bile-ducts.

In cases generally termed "congenital obliteration of the bile-ducts," such as those collected by Dr. John Thomson[2] and those described by later writers, a biliary cirrhosis of the liver seems always to be present. The occasional family tendency to the disease is very remarkable. Thomson[3] writes: "The parents of the patients seem generally to have been healthy people, and yet, in a considerable proportion of the cases, it is found that they have previously had one or more infants similarly affected. Instances are on record where as many as seven or even ten cases of infantile jaundice, apparently of this nature, have occurred in one family."

In regard to the pathogeny of these cases, in most instances the lumen of some portion of the bile-ducts is found completely obliterated, but in some cases no evident obstruction to the outflow of bile can be discovered. The exact site of the obliteration, when present, varies indefinitely. Thomson says that in at least one instance (Bouisson) of the disease a gall-stone was found, and this does not seem very surprising when we consider the more or less dependence of cholelithiasis on diseased conditions of the bile-ducts. Rolleston and Hayne[4] record an instance of the disease in a child who lived six months, and give references to cases not to be found in Thomson's monograph. They suggest that the disease is primarily started by poisons derived from the mother, and conveyed to the liver of

[1] Cf. Lereboullet, loc. cit., p. 418, Case 56.

[2] 'On Congenital Obliteration of the Bile-ducts,' Edinburgh, 1892.

[3] Allbutt's 'System of Medicine,' vol. iv, 1897, p. 253.

[4] "A Case of Congenital Hepatic Cirrhosis with Obliterative Cholangitis (Congenital Obliteration of the Bile-ducts)," 'Brit. Med. Journ.,' March 30th, 1901, p. 758.

the fœtus, and that a mixed cirrhosis and cholangitis are thus set up. This cholangitis, they say, by descending to the larger (extra-hepatic) bile-ducts induces an obliterative cholangitis analogous to obliterative appendicitis. In exceptional instances, they think, the obliterative cholangitis might be delayed and come on much later, such an event perhaps bringing Treves' case [1] (jaundice of sixteen years' duration from obliteration of the channel of the common duct, operated successfully in a girl of 19 years) into line with the others.

Since Rolleston and Hayne's paper, interesting communications have appeared on the same subject by J. E. Blomfield,[2] G. Parker,[3] and J. A. Arkwright.[4] Arkwright records a series of fourteen cases of icterus neonatorum amongst the fifteen children of one mother. Death occurred in ten of the cases. The four survivors were rather weakly, but lost their jaundice after a few weeks to several months. The mother herself had suffered from jaundice at the age of 4 years. It is remarkable that in the survivors no hepatic disease appears to have remained. However, F. J. Smith [5] has reported a case in which an infant recovered from icterus neonatorum in a fortnight, but developed biliary cirrhosis and died at the age of 4½ years. Moreover, the case of the girl J. S—, which I recorded, may really belong to the category of congenital cholangitis and biliary cirrhosis, for she was supposed to have been more or less jaundiced all her life, and died of biliary cirrhosis at 14 years of age.

Another clinical group of cases must here be alluded to. I have to thank Dr. A. Hall for kindly telling me about a remarkable case of congenital jaundice, described by H. A. Mason,[6] in

[1] 'Practitioner,' January, 1899. Judging from Treves' account of the progress of the case, the patient perhaps had some degree of biliary cirrhosis as well as the obstruction in the common bile-duct, for which the operation was successfully performed.

[2] 'Brit. Med. Journ.,' May 11th, 1901, p. 1142.

[3] 'Lancet,' August 24th, 1901, p. 520.

[4] 'Edinburgh Med. Journ.,' August, 1902, p. 156.

[5] 'Trans. Path. Soc. London,' 1890, vol. xli, p. 154.

[6] 'Quarterly Medical Journal,' November, 1902, vol. xi, p. 40. At the same meeting of the Sheffield Medico-Chirurgical Society at which Mason showed his case, Dr. W. T. Cocking showed a woman, fifty years old, in whom jaundice has been present since the age of three weeks, when it first appeared. No

a girl 13 years of age. She is fairly well grown, though somewhat backward for her years, and is without physical signs of disease in any of the thoracic or abdominal organs. The liver and spleen seem not to be enlarged. The fæces are said never to have been "clay-coloured," but the urine gives a slight Gmelin's reaction. The child's conjunctivæ (according to the mother) were yellow when she was three days old. It seems to me, in the light of the above-mentioned cases, that Mason's case can be best explained on the supposition that from intra-uterine cholangitis or primary developmental abnormality one (or more) of the intra-hepatic ducts has been blocked, or never was pervious. This would account for the persistent jaundice, and if only a small part of the whole gland is blocked no obvious enlargement of the liver or spleen need be expected; it would also account for the fæces being well coloured. Several cases described by French authors as "cholémie simple" and "ictère chronique acholurique" are of congenital origin, and probably of the same nature as Mason's case. In these cases the serum from a blister gives a Gmelin's reaction, but the urine is said generally to be free from bilirubin, though it may give a positive reaction during exacerbations of the jaundice. The liver and spleen are not necessarily enlarged, but one or both of these organs may be somewhat enlarged, at least during exacerbations of the jaundice. Widal and Ravaut[1] recently showed a man, 29 years of age, with congenital jaundice of this kind. The general health was well maintained. The urine was free from bilirubin, but contained urobilin. The fæces were well coloured. The serum from a blister gave a distinct Gmelin's reaction. I have at present under my notice a case which is clinically similar to these cases, except that the jaundice seems not to be congenital, but only of four or five years' duration. The patient is a girl about 18½ years of age.

pruritus or xanthoma. The liver is slightly enlarged, and a dilated gall-bladder can be felt. The spleen is not obviously enlarged. The fæces are little if at all paler than natural. The urine is high-coloured and gives a faint Gmelin's reaction. A child of the patient, born when she was forty-five years old, was healthy at birth, but developed jaundice after four weeks, and died at the age of fifteen weeks. Dr. Cocking, to whom I am indebted for permission to refer to the case, will shortly publish a full account. (The account appeared in the 'Quarterly Medical Journal,' February, 1903, p. 104.)

[1] Soc. Méd. des Hôpitaux,' Paris, November 21st, 1902.

Her blood-serum gives a definite slight Gmelin's reaction, and her urine, sometimes at least, also gives a faint one. Her fæces are well coloured. There is no obvious enlargement of liver or spleen. The girl is fairly well grown and plump, but temporary moderate pyrexia has been observed, and there is a tendency to bleeding from the nose and gums. I suspect that this case is of the same nature as Mason's and the French cases, though it is not congenital.

After this short digression I must return to the subject of congenital biliary cirrhosis. On the whole it seems that Rolleston and Hayne's case, and a number of the cases termed "congenital obliteration of the ducts," are examples of biliary cirrhosis due to a non-suppurative cholangitis,[1] just as the typical cases of Hanot's disease are. The peculiarity of the cases in question consists in the intra-uterine, or very early onset of the disease, and intra-uterine disease may in the bile-ducts, as in other parts of the body, give rise to secondary malformation and arrest of development.

Surely, however, it is quite probable that some of the cases of "congenital obliteration of the bile-ducts" are due to primary developmental malformation. In cases of congenital valvular disease of the heart we know that it may sometimes be difficult or even impossible to distinguish what is primary developmental malformation from the malformation and arrested development resulting from intra-uterine endocarditis; in the question of congenital obliteration of bile-ducts the same difficulty must arise. Needless to say, a decided family tendency to the latter condition, such as has been occasionally noted, implies the occurrence of what we may term a congenital "functional," if not organic malformation,[2]—that is, the occurrence of a "potential" disease leading afterwards to organic changes. More light will doubtless be thrown on the subject by subsequent observations.

In the so-called "congenital cystic disease" of the liver a striking microscopical feature is the excess of fibrous tissue in

[1] Doubtless, however, obstruction in the large bile-ducts, when present, is to be regarded as *one of the causes* of the biliary cirrhosis in these cases.

[2] In regard to possible relationship between hepatic cirrhosis and other chronic diseases on the one hand and developmental abnormalities on the other, cf. Hastings Gilford, "The Primary Disorders of Growth," 'Lancet,' 1900, vol. i, p. 1643.

the interlobular spaces. The distribution of this "congenital fibrosis" may be similar to that of the fibrosis in Hanot's disease, and it may therefore be suggested (for the liver as for the kidneys) that at least some cases of congenital cystic disease are the result of an attack of inflammation during intra-uterine life, from which the fœtus recovered. The very sharply defined margins of the fibrous patches between the hepatic lobules constitute, however, an objection to the inflammation theory, and point to the disease being a congenital adeno-cystomatous growth of the biliary ducts. Moreover congenital cystic disease of the liver has been found associated with congenital cystic disease of the kidneys and other organs, and with cleft palate and many other congenital malformations.

December 2nd, 1902.

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12. *A new pathogenic diphtheroid microbe*—Bacterium muris.

By E. Klein, F.R.S.

This microbe was derived from the hepatised lung of the white rat, and in morphological and cultural respects is related to the true diphtheria bacillus. Of two adult white rats which had been kept for some weeks in the same cage in the laboratory, one became spontaneously ill, and several days after was found dead. At the *post-mortem* the following condition was found:—One lung was almost completely hepatised; the other showed several patches of consolidation; in both lungs were petechiæ; the spleen and the liver were congested; the small intestine much congested, filled with sanguineous mucus and numerous gas-bubbles.

Film specimens made of the inflamed lung tissue showed numerous large and small clumps of cylindrical, thready bacilli, which, stained in methylene blue, show very pronounced metachromatism. In sections through the hardened lung the diseased parts showed the alveoli and infundibula filled with masses of fibrinous exudation, filled with leucocytes and red blood-corpuscles, and in these parts were found continuous

masses of the above bacilli. Cultures made with traces of the diseased lung tissue produced pure growths of the same bacilli; the same result was obtained by culture of the heart's blood.

The second (companion) rat died eighteen days later, and on *post-mortem* examination showed the identical appearances and the identical bacteriological result. The microbe in question is closely related to the Klebs-Loeffler bacillus both in morphology and in the appearances of the culture in the different media. It stains well after Gram, gives positive Neisser, and when stained in methylene blue shows metachromatic granules; some rods contain bright red globules. In glucose broth the microbe forms distinct acid. Injected into rats and guinea-pigs the microbe proves distinctly pathogenic; but a general infection with lethal end has not been achieved as yet. Large or small doses injected subcutaneously cause always the same local effect —viz. a firm tumour is produced in a few days after; this tumour increases considerably in size during the next ten or fourteen days, and either gradually disappears again or is transformed into an abscess. In the tumour and in the abscess the microbe is present in large numbers, as shown by film specimens and culture.

That our microbe, notwithstanding its great affinity in morphological and cultural respect and in respect of pathogenicity to the diphtheria bacillus, is really different from this latter is conclusively shown by experiments made with diphtheria antitoxin, for this has no neutralising power whatever when, previous to injection, it is mixed with a dose of the culture of the microbe. Animals injected with a mixture of the culture of the microbe and 400 or even 600 units of diphtheria antitoxin develop precisely the same local tumour abounding in the living microbes as does the culture alone in the control animals. Besides, adult rats, such as answer in a positive manner to the injection of our microbe, are refractory to even very virulent diphtheria bacilli. On account of the microbe being derived from the rat I propose for it the name "*Bacterium muris.*"

January 20*th*, 1903.

13. *A "diphtheroid" bacillus isolated from the uterus in two cases of puerperal fever.*

By Alexander C. R. Foulerton and W. F. Victor Bonney.

(From the Bacteriological Department, Middlesex Hospital.)

In the course of a series of cases in which a bacteriological examination of the contents of the uterus has been made after childbirth at full term and after miscarriage we have on two occasions isolated a bacillus which, from its morphological characteristics, may be included in the so-called "diphtheroid" group.

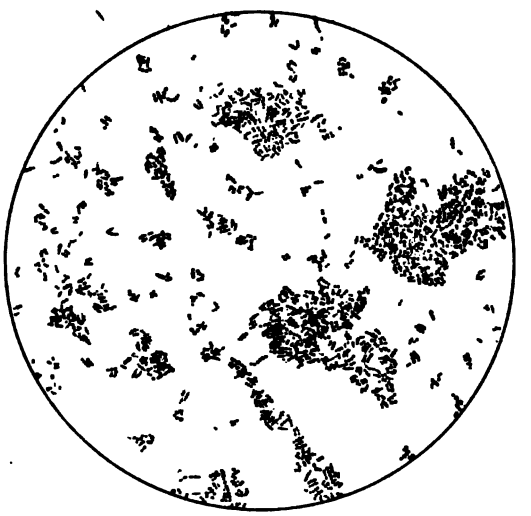
The clinical history in the two cases from which we isolated this bacillus, and the circumstances under which it was isolated, were briefly as follows:

Case 1.—The patient, a multiparous woman, had passed through a normal confinement, but on the fourth day afterwards there was a sudden rise of temperature with some headache. The lochia were somewhat offensive, the uterus was tender on abdominal palpation, the temperature ranged between 103° and 104° F.

With the use of intra-uterine douches the temperature fell on the seventh day after the confinement, and the patient made a good recovery. On the fifth day after confinement a series of culture tubes were inoculated from the fundus of the uterus, and another series from the vagina. A pure culture of the bacillus referred to was obtained on all the tubes inoculated from the cavity of the uterus. From the contents of the vagina four species of bacteria were isolated: (1) a bacillus identical with that found in the uterus, (2) a species of coccus which resembled *Staphylococcus pyogenes albus*, and (3 and 4) two species of bacilli which grew freely on gelatine at a temperature of 22° C. without liquefying the medium, which stained by Gram's method, but which we failed to identify as belonging to any species with which we are familiar.

CASE 2.—This patient had a miscarriage during the second month of her pregnancy. Pyrexia developed a few days after the miscarriage and continued for several weeks; the temperature ranged between 104° and 105° F. at the time when the cultures were obtained. The patient made a slow recovery. On the fourteenth day after the miscarriage a series of tubes were inoculated from secretion in the cervical canal, the material being taken from as high up as possible. Two species of bacilli were obtained on the tubes inoculated: (1) an organism identical with that isolated in pure culture from the cavity of the uterus in the first case, and (2) a short bacillus which grew freely on

FIG. 12.



Culture on blood-serum; 72 hours' growth at 37° C. × 750.

gelatine at a temperature of 22° C. without liquefying the medium, and stained by Gram's method. In the case of this organism again we failed to identify the exact species.

The special organism which we isolated in these two cases has a definite morphological resemblance to *B. diphtheriæ*, and evidently belongs to the "group" of which the latter organism is the best known type.

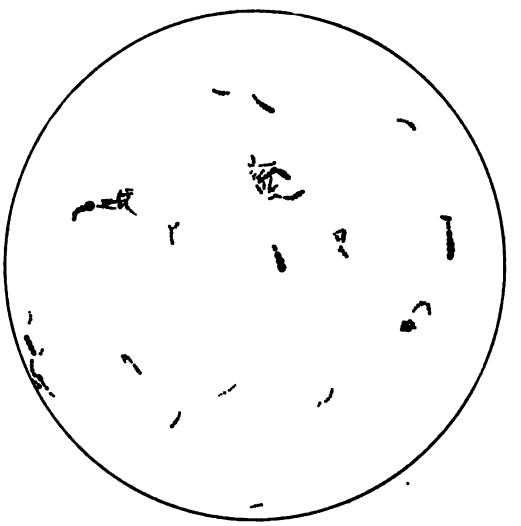
Morphology.—The morphology of the bacillus varies considerably according to the medium on which it is grown.

On inspissated horse serum.—The general morphology of the

organism corresponds closely with that of *B. diphtheriæ* when growing on the same medium, except that the rods are, speaking generally, rather coarser and larger. The organism appears as shorter or longer rods, which either present a beaded appearance or stain equally throughout their length; "coccal," "pear-shaped," and "Indian-club" forms are also found. This description applies to cultures of from twenty-four to seventy-two hours' growth at 37° C.

On nutrient agar.—The morphology is very irregular, and cultures of twenty-four hours' growth on this medium show a

FIG. 13.



Culture on agar; three months' growth. × 750.

Note.—The preparations from which the photographs were taken had been stained by Gram's method without the use of a counter-stain. As the portions of the bacillus between the granules tend to become decolourised by the alcohol, the "coccal" appearance of the preparation is slightly exaggerated.

variation of form similar to that which may be seen in old cultures of *B. diphtheriæ* when growing on horse serum. Thus there are "Indian-club" forms, short, oval, and spherical forms, long, beaded forms which when stained by Gram's method appear as short chains of cocci, there are "spindle" forms, bulky, "pear-shaped" forms, and, in short, every possible variation.

In *pepton beef broth* variation of form is less marked than on agar, and cultures show a predominating number of rods

which stain evenly; but beaded, oval, and spindle-shaped forms may be seen.

In cover-glass specimens which have been prepared and stained in the ordinary way the general grouping of the bacilli resembles that seen in a similar preparation of *B. diphtheriæ*, —that is to say, there is a tendency for the rods to be massed together in small clumps, and to present a palisade arrangement. The bacillus is non-motile. Spore formation has not been observed.

Staining characteristics.—The bacillus stains well with the ordinary aniline dyes, and retains the stain with the methods of Gram and Claudius. With Loeffler's methylene blue the presence of deeply staining granules is well marked. Contrast staining was not obtained with Neisser's method. No portion of the organism is acid-fast.

Cultural characteristics.—Growth occurs most freely at a temperature of about 37° C. At 22° C. growth is feeble and uncertain, and frequently does not occur. Growth occurs under both aërobic and anaërobic conditions, but more freely under the former.

On gelatine at 22° *C.*—Growth is very slow, scanty, and uncertain; after a week's incubation there may be a few small, white, opaque, circular colonies on the medium.

On nutrient pepton agar.—In a smear culture at 37° C. growth appears after twenty-four hours as a fine layer of confluent growth, slightly raised above the surface of the medium, and having on the surface the appearance of ground glass. In a culture in which the growth has been very lightly rubbed out, delicate, isolated colonies with a dull surface, like that of ground glass, are seen. At 22° C. the amount of growth on agar is very scanty after one week's incubation.

The addition of glucose or maltose to the medium has apparently no influence on growth; the addition of glycerine has, if anything, a slightly inhibitory effect.

On inspissated horse serum.—Growth on this medium resembles that obtained on agar, but is rather more active, and the resulting layer is rather more opaque.

In *pepton beef broth* at 37° C. growth is comparatively slow. After forty-eight hours' incubation there are a number of very fine, sand-like granules at the bottom of the tube, together with

more or less filmy-looking *débris*. The broth above the deposit remains quite clear. The broth shows the presence of a distinct trace of indol after six days' incubation.

With neutral litmus glucose pepton broth there is no colour reaction after six days' incubation at 37° C.

In faintly alkaline *litmus milk* growth occurs, but there is no obvious alteration of the medium after ninety-six hours' incubation at 37° C.

On natural *potato* fairly free growth occurs, showing itself as a fine, spreading, moist-looking layer.

Thermic death-point.—The organism survives exposure to moist heat at a temperature of 65° C. for ten minutes, and is destroyed by an exposure of the same duration at a temperature of 70° C.

Pathogenicity.—The culture obtained from the first case was tested on guinea-pigs, rats, mice, and rabbits; but no obvious pathogenic effects were produced, either generally or in the way of local reaction, when the organism was injected into the subcutaneous tissue.

Similar negative results were obtained from the culture grown from the second case.

Whilst we think that, because of its general morphology and cultural characteristics, this organism may conveniently be placed in the same group of bacilli as that to which *B. diphtheriæ* belongs, it is at the same time easily distinguished from that organism by, amongst other points, its somewhat larger size, the absence of any pathogenic action on the guinea-pig, and the non-occurrence of acid in cultures grown in glucose pepton broth for several days.

It seemed probable that the bacillus was pathogenic in the two cases from which we isolated it, although, of course, we have no direct proof that this was so. We have not met with any other organism of this group in any other of the cases in which we have examined the contents of the uterus itself under similar conditions. But we have on several occasions found a somewhat similar bacillus in the secretion of cases of catarrh of the cervical canal.

The only reference bearing closely on the subject which we have been able to find is in a paper by Haultain,[1] of Edinburgh,

[1] Haultain, 'Transactions of Edinburgh Medical Society,' vol. xxii, p. 189.

who described the finding of *B. diphtheriæ* itself in the uterus after confinement. Haultain does not give in his paper any details of the steps taken to identify *B. diphtheriæ* in this case; but he has been so good as to supply us privately with the information, and it would appear that the identification of the organism was a satisfactory one. In other cases in which *B. diphtheriæ* has been found in the genital tract of puerperal women, the infection has been primarily a vaginal one with the formation of false membranes.

It is not impossible that the bacillus which we have described is related to the so-called "diphtheroid" organisms which have been described as occurring in cases of noma vulvæ. One of us has recently isolated a closely similar organism from a case of phagedena of the penis, and we have also met with a somewhat similar bacillus in a case of cancrum oris.

January 20th, 1903.

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14. *A specimen of congenital tuberculosis.*

By F. W. Andrewes.

Authentic cases of congenital tuberculosis in human infants are so rare that every specimen should be placed on record. Nothing is now known as to the history and antecedents of the specimen shown. It was added to the museum of St. Bartholomew's Hospital some time between 1846 and 1862, *i.e.* at a time when the rarity and importance of the case would have escaped remark. No one seems to have paid any attention to it since. The specimen consists of an infant's thoracic viscera. The pulmonary artery has been injected with vermilion, which has penetrated all the capillaries of the lung; the tracheal and bronchial glands are very much enlarged, and in a condition of caseation. Typical miliary tubercles are scattered through both lungs, and are well seen both on the cut surface and beneath the pleura. Microscopic sections of the lung and bronchial glands show the characteristic structure of tubercle. The only information vouchsafed in the old museum catalogue is that the infant

died shortly after birth. There is no reason for doubting the truth of this. The organs are of the size natural to a child at birth; they are not those of a child several months old. And fortunately the heart and vessels are present to confirm the statement. The foramen ovale is closed, but the ductus arteriosus, though closing, is still patent. The lungs are expanded. The specimen therefore contains internal evidence that the statement made concerning the date of death is correct, and it may fairly be concluded that the infant died not many days, and certainly not more than a week or two, after birth. Yet the tuberculous lesions in the mediastinal lymphatic glands are indisputably of much greater duration than this; the great size of the glands, and the advanced caseation which they show, indicate a tuberculous process of many weeks, probably of at least a month or two's duration. The miliary tubercles in the lungs are more recent, but even these are probably of ante-natal date. It is much to be regretted that nothing is recorded of the condition of the mother and of the placenta. If the congenital nature of the tuberculosis be admitted, one point calls for comment. In post-natal infection primary tubercle of the bronchial and tracheal glands is so common, and so readily explained by inhalation of tubercle bacilli through the respiratory avenues, that it is somewhat of a shock to find a precisely similar primary focus, which must have originated long before the fœtus had ever drawn a breath. Two paths of infection are possible. The bacilli may have gained access to the fœtus from the placenta by the blood-stream; in this event lodgment in the mediastinal glands must have been a pure accident. It seems more likely that from the placenta tubercle bacilli gained access to the liquor amnii, and thus passed into the mouth of the embryo. It is well established that a fœtus frequently swallows amniotic fluid, and it is not difficult to believe that the fluid may have passed into the trachea. Such an explanation of the specimen brings it more into harmony with what is known to be the path of infection in such cases after birth. *January 6th,* 1903.

15. *Two specimens of rare forms of congenital malformation of the heart.*

By F. W. Andrewes.

These specimens have been in the museum of St. Bartholomew's Hospital, one for more than fifty, and the other for more than eighty years. Yet till now they have not been adequately dissected or described, so that they have all the interest and value of new specimens. The method employed in their dissection has been to stitch up all incisions, so as to bring the heart as nearly as possible back to its original shape. The cavities are then exposed by cutting large rounded windows in the anterior walls of the ventricles, aorta, and pulmonary artery, and in the posterior walls of the auricles. In this way the cavities and orifices can be well displayed (with the sole exception of the aortic orifice).

Case 1. *Absent right auriculo-ventricular orifice, with rudimentary right ventricle. Double left auriculo-ventricular orifice.*—The heart is that of an infant which died at seven weeks. The greater part of the organ is formed by the left ventricle, which is thick-walled and capacious, and gives rise to a normal aorta. The right ventricle is a mere rudiment perched on the shoulder of the left; its cavity is no bigger than a large pea, but the conus arteriosus, though small, is not so small in proportion. The pulmonary artery is small, but there is no pulmonary stenosis; the valve shows three fragile cusps which are not adherent. The ductus arteriosus is so nearly closed that a bristle can only be passed part of the way along it. There is a small gap in the upper part of the septum ventriculorum. The foramen ovale is widely patent. The right auricle is of normal size, but has in its floor no trace of any auriculo-ventricular orifice, or any direct communication with the rudimentary right ventricle; the venæ cavæ opening into it are normal. The floor of the left ventricle, on the contrary, presents two distinct auriculo-ventricular orifices, nearly equal in size, and situated one behind the other. They are separated by a stout fibrous septum, and each has its own well-developed valve-curtains and

chordæ tendineæ attached to different papillary muscles. Both open into the left ventricle. Seen from above, the two orifices are distinct, but on the ventricular aspect there is some slight fusion of the valve-curtains. A conceivable explanation of this very rare condition may be hazarded. The primitive communication between auricle and ventricle is divided into two by the coalescence of two prominences of connective tissue, which grow out, one from the front and one from the back of the originally single channel. The bridge thus formed is the "septum intermedium" of His. The "septum superius" growing down from above and dividing the auricles, and the "septum inferius" growing up from below and dividing the ventricles, ought to fuse with the septum intermedium and complete the separation between the right and left cavities of the heart. If, by any chance, the superior and inferior septa became deflected and fused with the primitive heart wall to the right side, instead of with the septum intermedium, the condition shown in this specimen would be produced—a total absence of communication between the right auricle and ventricle and two orifices on the left, separated by the isolated septum intermedium. The number of cusps in the auriculo-ventricular valves in the specimen is too ill-defined to enable one to say with certainty that one is bicuspid and the other tricuspid.

Case 2. *Atresia of the conus arteriosus of the right ventricle by a stout muscular septum, perforated only by a minute aperture.* —The heart is that of an adult who survived to the age of 28 years. It was added to the museum of St. Bartholomew's Hospital some time before the year 1831, and nothing is now known as to the clinical history of the case. The two ventricles are nearly equal in size and in the thickness of their walls; they contribute almost equally to the formation of the broad, blunted apex. There is a wide defect in the upper part of the interventricular septum. Where the body of the right ventricle should pass into the conus arteriosus, it is separated from it by a muscular septum, at least a quarter of an inch in thickness, and continuous with the ventricular wall. The conus arteriosus is thus separated off as a distinct muscular chamber, triangular in shape, and with rudimentary columnæ carneæ in its walls. This chamber passes above into the pulmonary artery; the

pulmonary orifice is small but not locally narrowed; its valve presents only two cusps, scarcely thickened or coherent. The sole communication between the right ventricle and the pulmonary artery is by a minute rounded aperture in the abnormal muscular septum above mentioned. This aperture just admits a good-sized probe, and presents some calcareous deposit. A few partially calcified vegetations are present on the wall of the conus above it, and there are also some small vegetations on the tricuspid valve. The tricuspid and mitral valves are otherwise natural. The foramen ovale and the ductus arteriosus are unfortunately not preserved in the specimen, so that their condition is unknown. But it is difficult to believe that the patient can have survived to the age of twenty-eight years without some other blood-supply to the lungs than that presented by the minute orifice in the muscular septum seen in the specimen. In spite of the evidence of secondary endocarditis, it is plain that this extremely rare form of pulmonary stenosis depends directly upon developmental abnormality, and not, as is believed to be the case in most instances of the condition, upon a fœtal endocarditis. *January 6th,* 1903.

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16. *Occlusion of the innominate artery without subsequent thrombosis.*

By H. Thursfield.

The specimen (from a man aged 47) consists of that part of the arch of the aorta from which arise the three main branches. These are seen apparently normal in situation and size. The aorta was itself the seat of an aneurysm, the rupture of which had caused sudden death. The wall of the aorta is extensively diseased; the endarteritis is, however, of a somewhat unusual character; it does not show the "atheromatous ulcers" and calcareous plates which are so often seen in the walls of aneurysmal sacs, but presents an almost smooth surface slightly nodular, but without any distinct breach in the surface. The orifice of the left subclavian is surrounded by a slightly yellower

patch of endarteritis, but is widely open; that of the left carotid is reduced to the size of a pin-head, though the artery itself remains of normal size and shows no traces of thrombosis. The same change has gone on to a further extent in the case of the innominate artery; here there is not only no orifice at all to be seen on the aortic wall, but there is not even a dimple or pucker in the surface to betray the spot at which it was situated. Here again also the innominate artery has remained of a natural size, and there is no trace of clotting; a probe passes down to the aorta without any obstruction.

A case identical in nearly all respects was reported to the Society by Dr. Spencer Watson in the year 1868 ('Path. Soc. Trans.,' vol. xix, p. 170). The patient was aged 56, and three years before death it had been noted that the left radial pulse was smaller than the right. The patient died in an attack of angina. At the *post-mortem* examination it was found that "the orifice of the left subclavian artery was completely closed, though its canal was pervious up to the point of origin from the aorta."

The two points of interest which present themselves in these cases are—first, the nature of the endarteritis which can thus close up a large orifice in the wall of the aorta; and secondly, the reason why the blood between the orifice and the first branch did not coagulate. In respect of the endarteritis, I suppose it must be considered as a form of obliterating endarteritis, though one is more familiar with this in smaller arteries than the innominate and subclavian. With regard to the second point, I cannot advance any explanation for the absence of thrombosis. *December 2nd,* 1902.

17. *Dermoid cyst of the inguinal canal.*

By Herbert J. Paterson.

This cyst was removed from the inguinal canal of a gentleman aged 35. A swelling, thought to be hernial, had been noticed in the right inguinal region for five years. Three weeks before

I saw the patient the swelling had suddenly become painful, and an attempt had been made to reduce it under an anæsthetic. The swelling was elastic, oval in shape, about three inches in length, with its long axis in the line of the inguinal canal. It extended somewhat inwards over the front of the pubic bone. The external abdominal ring was large, readily admitting the tip of the finger, which impinged upon the swelling lying apparently in the inguinal canal. On cutting through the aponeurosis of the external oblique muscle, an opaque whitish swelling was exposed. The swelling was incised, and thick pultaceous material escaped. Further examination showed the swelling to be a closed sac, not communicating with the abdominal cavity. The sac was dissected out, and it was found to be firmly adherent to the neighbouring structures. There was no hernial sac existing, but there was a considerable gap in the muscular wall of the abdomen, between the arciform fibres and the conjoined tendon on the inner side, and Poupart's ligament below. Posteriorly, in its outer two-thirds, the cyst lay in contact with the subperitoneal fat in the gap above described, while its inner third lay in contact with the anterior surface of the pubic bone, to which it was attached by a firm fibrous band. Inferiorly, the cyst lay close to the grooved superior surface of Poupart's ligament, part of the cyst wall extending deeply and being adherent to the femoral vein. Anteriorly, the cyst was covered by the aponeurosis of the external oblique muscle.

The cyst measured two and three-quarter inches by one inch. A single hair was found on the interior of the anterior wall. Microscopically, a section of the cyst wall shows—

1. Epidermis, with a well-marked stratum squamosum, a stratum epitrichiale, and a deeper layer of more deeply staining cells.

2. Cutis vera of connective tissue, the superficial layer of which shows no papillæ.

Cysts of the inguinal canal have been described as "dermoids," but, as Bland-Sutton remarks (1), "the records are not to be relied on." Cysts have been assumed to be dermoid on no other evidence than that they contained pultaceous material. Notwithstanding a careful search I have been unable to find a single case in which the wall of the supposed dermoid was submitted to microscopical examination. It is noteworthy that

Lannelongue and Achard (2) do not even mention dermoids of the inguinal canal. In the literature of recent years, the only case of supposed dermoids in this region which I have been able to find is one reported by Pearce Gould (3), but there were no hairs in the sac, and the wall of the sac was not examined microscopically.

REFERENCES.

1. *Bland-Sutton.*—'Tumours,' 2nd ed., p. 353.
2. *Lannelongue and Achard.*—'Kystes Congénitaux,' 1886.
3. *Pearce Gould.*—'Lancet,' Nov. 4th, 1893, p. 1127.

June, 1902.

Report on Mr. Paterson's Dermoid Cyst from the Inguinal Canal, by the Members of Council representing Morbid Anatomy. —We have examined the cyst exhibited by the author, and the microscopic sections submitted to us, which we have supplemented by others prepared by ourselves.

The author describes the cyst wall as lined by "epidermis, with a well-marked stratum squamosum, a stratum epitrichiale, and a deep layer of more deeply staining cells." This description does not appear to us as complete as the rarity of the specimen would demand. We regard the epidermis as constituted superficially by a stratum corneum, beneath this by a narrow stratum granulosum, and beneath the latter by a Malpighian layer in every way normally constructed, its more superficial cells being flat, its deeper polyhedral, and its deepest vertically elongated.

We differ from the author in his view as to the presence of a stratum epitrichiale. We regard the spaces in the stratum corneum not as within cells, but as due to artificial delamination of the layer. We do not consider that an epitrichial layer is present. In places where the edge of the section has become turned in the mounting, the horny material appears as long narrow ribbons. The simulated cell-distension is wanting, moreover, in sections made by ourselves without the employment of paraffin. In such sections we may notice, also, that the deep palisade series of cells is throughout vertically disposed, whilst the disposition is only here and there apparent in the sections submitted by the author. The sections prepared by ourselves

were made especially, however, with the object of studying the elastic tissue present in the corium of the cyst wall, and for this purpose they were stained with Unna's acid orceïn. They exhibit a notable amount of the tissue in question. In the deepest part of the corium the elastic fibre is sparsely distributed amongst the bundles of white, and is itself comparatively coarse in texture; in the immediate neighbourhood of the epidermis it forms a fine, very conspicuous brushwork of fibrils intimately mingled with the fibres of the white kind.

We consider, therefore, that the cyst may be classified as a dermoid. The presence of a stratum granulosum in its epithelium serves to distinguish it from a mucosal cyst or one formed of mucous membrane, whilst the large amount of elastic tissue in the corium, and the thickness of the corium itself, not only indicate its cutaneous relationship, but differentiate it from such a cyst as might arise in a hair-follicle.

As to the origin of the cyst, the author offers no suggestion. Having in view the attachment of its inner end to the symphysis pubis, and the fact that it occupied only the very lowest portion of the inguinal canal, it may be surmised that the cyst arose in connection with the median closure of the abdominal wall.

T. W. P. LAWRENCE.
S. G. SHATTOCK.

(Signed) H. MORLEY FLETCHER.

On behalf of the Members of Council representing the section of Morbid Anatomy, November, 1902.

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18. *A case of primary sarcoma of the lung.*

By E. P. BAUMANN and F. A. BAINBRIDGE.

History.—Edith A—, aged 3 years and 11 months, was brought to the Hospital for Sick Children, Great Ormond Street, on June 30th, 1902, on account of cough and hæmoptysis. She was admitted under the care of Dr. D. B. Lees, to whom we are indebted for permission to publish the case.

The past history was that the child had been ailing for six weeks. The illness began with headache and complaints of pain in the abdomen after food; soon afterwards she became feverish and developed a cough. Two weeks after the onset she spat up blood during a fit of coughing. "The blood, which was mixed with matter, poured through the nose and mouth, and continued to do so for five or six minutes after the cough stopped." A similar attack of hæmoptysis occurred the same night, and was repeated during the next four or five evenings. No further bleeding took place until the day before admission, when "a clot of blood came from the nose." During the last few days the cough had been worse, the child was irritable, refused her food, and complained more of headache and pain in the abdomen. She had lost flesh to a considerable extent since the onset of the illness. There was never vomiting or diarrhœa.

Before the present illness the child had been in good health, with the exception of an attack of whooping-cough six months before, which had left her with discharging ears. She was one of a family of six, of whom one was stillborn and two had died,—one of an "abdominal operation," the other of "abscesses in the head." No tendency to hereditary disease on the part of the parents was elicited.

State on admission.—On admission the case appeared to be a clear one of effusion into the left pleura. The child was pale, and looked very ill; she lay on her left side. Considerable respiratory distress was present, and there was a frequent shallow cough. The temperature on admission was 101·4° F., the pulse 132, respiration 68. The whole of the left side of the chest was dull to percussion, and the breath-sounds, vocal resonance, and vocal fremitus deficient or absent. The intercostal spaces bulged, and there was some dilatation of the superficial veins. The heart was displaced considerably to the right.

Course of illness.—Shortly after admission the child was anæsthetised, and an exploratory needle inserted in three places in the neighbourhood of the angle of the left scapula, but only a little blood-stained fluid obtained. An incision was then made through an intercostal space into the pleura with no further results. A tube was left in the wound.

On July 1st, the day following admission, distinct physical signs of pneumothorax developed over the front of the chest.

On July 2nd aspiration was performed in the middle of the left axilla, and a little frothy blood-stained fluid drawn off containing some fragments of cheesy *débris*. No evidence of malignant growth could microscopically be found in these, and examination for tubercle and other organisms proved negative.

On July 4th an exploratory syringe was again introduced at the left posterior base, this time with no result.

The pneumothorax still persisted, pulse and respiration rate remained high, and the pyrexia maintained an irregular course, ranging between 97° and 100·8°; there was never any expectoration. The general condition of the child became rapidly worse, and death occurred on July 12th, a fortnight after admission. The whole duration of the illness was eight weeks.

Post-mortem examination.—At the necropsy the upper lobe of the left lung was found to be replaced by a soft odourless growth of friable, brain-like consistence, with large blood-clots on its surface. The whole was shrunken and small, leaving a considerable space in the upper half of the left chest. The lower lobe was collapsed and firm, but showed no signs of invasion by the new growth. The left pleura was adherent all round, and thickened by fibrinous exudation, but no nodules were found, and it appeared to be quite free from any new growth. The right lung was emphysematous, with patches of collapse. The bronchial and mediastinal glands presented a healthy appearance, and no secondary growth could be discovered in any other tissues or organs.

On histological examination the growth in the left upper lobe was found to be sarcoma of the round-celled variety.

Primary sarcoma of the lungs is a very rare disease. The *post-mortem* records of the Hospital for Sick Children, from January, 1860, to the present day, do not furnish a single other instance of its occurrence. Drs. Rolleston and Trevor, who recently described a case which had occurred at St. George's Hospital, were able to find records of only seven other instances of this condition. *February 17th*, 1903.

19. *Carcinoma of the thoracic duct.*

By W. T. Hillier.

For permission to show this case I am indebted to the courtesy of both Dr. A. F. Voelcker and Dr. R. A. Young.

The case is that of a married man aged 61, a pocket-book maker, who was admitted under the care of Dr. Voelcker in August, 1902. His family history gives no record of tuberculosis, syphilis, or cancer; both his parents lived to over eighty. Of previous illnesses he had a mild attack of typhoid fever ten years ago, and was ill four weeks with it. He has had four attacks of influenza followed by bronchitis. The last of these was five years ago. Since one of these attacks, in 1891, he noticed wasting of the thumb muscles, but no inconvenience as loss of movement or muscular twitchings. Eighteen months ago he was laid up for two months with pneumonia, which left him very weak, and since that time he has felt ill. He dates his present illness from the beginning of 1902, when he began to have pains right across the upper part of his abdomen. He has never vomited or felt sick from them. The pains are a dull aching, sometimes griping; they are always continuous. For the last ten days or so he has rapidly lost weight. The following is the description of his condition on admission:

The patient is an old man with sunken cheeks. There is wasting of the muscles of the hand—interossei and lumbricales,—especially on the right side. Wasting is more marked on the extensor than on the flexor aspect. There is great loss of tone in the abductors and flexors of the thumb. Knee-jerks appear to be absent on both sides. Pupils react to light and accommodation. Temp. 99°.

Respiratory system.—There is well-marked wasting of the respiratory muscles exposed to view, but there is good movement on both sides. Palpation reveals absence of vocal fremitus from the left infra-clavicular region. There is no abnormal impairment of resonance on percussion in any part of the chest, which, in fact, is hyper-resonant. On auscultation there is

tubular breathing heard on the left side beneath the clavicle. The breath-sounds over the left upper lobe at the back are weak.

Cardio-vascular system.—The heart's apex-beat is in the sixth left interspace, half an inch internal to the nipple line. The superficial cardiac dulness has the following boundaries:—above the fourth rib internally, the left border of the sternum, below the seventh costal cartilage. No murmurs are heard. The first sound at the apex is clear. No sounds heard at the base owing to emphysema. Pulse: good volume, moderate tension, artery atheromatous. Urine alkaline, sp. gr. 1020, is very highly coloured, contains albumen; no sugar, pus, or blood. His appetite is poor, tongue slightly furred, teeth in very bad condition. Bowels very constipated. He always has a dragging pain on defæcation. No sickness. Over the abdomen, in left hypochondrium and stretching over epigastric and a small part of the umbilical region, he feels a dull aching pain which is continuous. A prominent vein can be seen in the middle line running up over the front wall of the abdomen to beneath the ensiform cartilage. Hard lump felt below left costal margin. Lower border of liver not felt.

During the time he stayed in the hospital, till he died on September 23rd, his chief symptoms were obstinate constipation, marked emaciation, and the appearance of secondary growths. The note of August 21st is of interest—"appetite better, but directly he moves he feels pain over the abdomen." The intercostals on the left side have wasted to a much greater extent than those on the right side. There is a more uniform hardness over the anterior wall of the stomach, but the lump felt before has not diminished. The lower border of the liver is on a level with the umbilicus. A week or so later an umbilicated nodule in the liver could actually be seen to be present.

During his illness his temperature was practically normal, falling a little at the end. The pulse-rate slightly increased in frequency as the case progressed.

Autopsy.—The *post-mortem* examination was made by Dr. R. A. Young, to whom I am indebted for the notes from which the following are abstracted, and also for much other valuable assistance in the preparation of this paper. There is extreme emaciation, with cachectic appearance and slight jaundice.

The small muscles of the hand, and notably the abductor indicis, are particularly wasted.

On the posterior wall of the bowel, about six inches above the anus, is a rather firm ulcerated mass, rather larger in area than half a crown. It does not involve the whole circle of the gut. The central part of the growth is adherent to the posterior wall of the pelvis.

From this mass of new growth there is a continuous chain of enlarged glands; first, those behind the rectum and in the mesosigmoid, then the iliac, then the mesenteric and aortic, which form an enormous mass about the mid-line of the abdomen. These glands are caseous and soft on section.

The aorta is almost completely surrounded by new growth. On removing the aorta and mass of glands surrounding it the bodies of second and third lumbar vertebræ are found to be largely replaced by softened new growth. Opposite the second lumbar vertebra is found the greatly enlarged receptaculum chyli and its tributaries, filled with new growth.

From this point the thoracic duct is continued up through the diaphragm as an irregularly thickened tube or stem, and ends as a wide, flattened tube lying over an enlarged soft left supra-clavicular gland.

The bronchial lymph-glands are markedly enlarged. Secondary growths occur in the lungs and in the liver. In the lungs the deposits of growth are scattered throughout as soft masses an inch or more in diameter. In the liver they form enormous umbilicated masses, and cause great enlargement. The organ weighs 156¼ oz., and occupies the hypochondriac regions and the epigastrium. In the peritoneum are only a few ounces of slightly blood-stained fluid, not chylous. In the right pleural cavity are 16 oz., and in the left one 12 oz. of clear fluid. There is a slightly increased amount of clear fluid in the pericardium. The heart presents a condition of brown atrophy, has thin walls, and there is atheroma of the mitral and aortic valves. The following organs appeared to be healthy:—the kidneys (right weighs 4¾ oz., left weighs 4½ oz.), the spleen (small, weighs 2½ oz.), the pancreas, supra-renal capsules, thyroid gland, larynx, trachea, and bronchi.

Microscopically the growth in the rectum appears to be a columnar-celled carcinoma, although the actual amount of

FIG. 14.

A B

A photograph of the thoracic duct described in the text. A, the upper half, showing the termination of the duct on an enlarged supra-clavicular gland. B, the lower half of the duct and its tributaries; at the lowest part is shown an enlarged lumbar gland. [Slightly reduced: the upper end of B is continuous with the divided lower end of A, the figures giving the entire length of the duct, which as so reduced is 39 cm.]

columnar-celled formation is rather small, and spheroidal cells are very abundant. There also appears to be considerable degeneration of the cells. The liver, lungs, and lumbar lymph-glands are infected by similar growth. The thoracic duct appears filled with new growth, and its walls infiltrated. Moreover no lining layer of cells can be distinguished, so that the cells of the new growth seem to be attached to the walls of the vessel. The cells here appear to be spheroidal. Groups of these cells are also seen in spaces in the wall of the duct.

Other instances where a condition of this nature has been found at the autopsy present a most remarkable similarity in that there are no symptoms to indicate the condition—not even chylous ascites.

Moreover the illustrations given of the specimens leave no doubt as to the identity of the nature of this case, and figures of sections also show appearances so alike that it would seem to be a pathological condition of a very definite type.

M. Troisier records three cases ('Bull. et mém. Soc. Méd. d. Hôp. de Paris,' 1897 and 1898).

The first occurred in a man aged 34, whose illness lasted about nine months. The primary growth is said to have probably begun in the left adrenal, but of this there is no absolute proof. At the autopsy the left kidney and adrenal formed a bulky tumour. Large distended lymphatics in fat around the kidney. The lumbar and glands along the aorta were infected. Dilated lymphatics also occurred in the lungs, especially just around some secondary growths. The bronchial lymph-glands and the left supra-clavicular gland were infected, posterior mediastinal glands infected, and the thoracic duct. No lesion of heart or aorta. No infection of axillary or inguinal glands. Right kidney, adrenal, bladder, prostate, testicles, liver, stomach, and intestines all seemed healthy. The diaphragm appeared absolutely healthy on both aspects.

The second case was that of a woman aged 50, who had the primary disease in the uterus involving the broad ligaments. Secondary growths occurred in the pelvis of the left kidney, peritoneum, liver, lumbar, aortic, and left supra-clavicular gland, and the thoracic duct. No microscopical examination was made of this case.

The third instance occurred in a woman aged 53. The

primary growth was in the lesser curvature of the stomach, and involved the pancreas. Secondary growths occurred in the liver, omentum, mesenteric and aortic glands, lungs, bronchial, tracheal, and anterior mediastinal glands, right femur, and in the thoracic duct. Microscopically the thoracic duct appeared filled by polymorphous epithelial cells, while two or three layers of large cells with large nuclei were seen implanted on the internal endothelial lining like endothelial cells.

Unger ('Virchow's Archiv,' Band cxlv) relates a case where this condition was met with. The patient, a woman aged 49, died from carcinoma of the uterus. Secondary growths occurred in the liver, left kidney, mediastinal and left supraclavicular glands, and in the thoracic duct, which was one of a twisted bundle of cord-like vessels. Microscopically the growth appeared as a squamous-celled carcinoma showing alveolar arrangement; no cell nests. He describes the remarkable appearance of sections of the thoracic duct where it is completely thrombosed; its wall is surrounded by adipose tissue, in which a few epithelial and round cells are present. The peripheral part of the wall is of nearly normal appearance; the inner part is only covered with normal endothelium in a few spots. Collections of cancer cells are frequently present, which are grown with the cells of the inner coat without distinct demarcation. The lumen is chiefly filled with fibrin threads, which in places adhere to the wall. To a less extent it is filled with collections of cancer cells. The cells lining the wall have a columnar form.

Unger states that about ten cases were at that time (1896) on record.

Weigert ('Virchow's Archiv,' Band lxxix) records a case in a man aged 57. The primary growth was a columnar-celled carcinoma of the rectum, and there was infection of the liver, inguinal, pelvic, and retro-peritoneal lymph-glands, and the thoracic duct.

He believed the duct to have been infected from the lymph-glands overlying it at the diaphragm.

No enlargement of the lacteals or mesenteric lymph-glands,—in fact, only the channels in the immediate connection with the duct were enlarged.

In all these cases there was practically no chylous ascites,

although in Unger's case there was 100 c.c. in the peritoneum of turbid fluid and similar fluid in both pleural cavities; but then this case also seems to have differed from others in that not only the thoracic duct, but several lymph-channels in the thorax which coursed along with it were similarly distended. Weigert's case rather differs from the others in the absence of distended lymph-channels connecting the primary growth with the thoracic duct, or even with the lymphatic glands.

None of the cases appear to have had symptoms giving rise to suspicion of the condition, unless the enlargement of the left supra-clavicular lymphatic gland or glands be taken as such. That it should not be is evident when one reflects on the rarity of the thoracic duct infection and the comparative frequency of infection of the left supra-clavicular gland.

As to the cause of the infection of the thoracic duct, Troisier seems to think this condition is the result of a reaction on the part of the lining cells of the duct as well as an infection by the cells of the new growth. There seems, however, no reasonable ground for calling it a lymphangitis. Yet it is remarkable that no distinction can be made between the lining cells of the duct and the cells of the new growth.

The enlargement is also remarkable. This is comparable to enlargement of lymphatic glands by carcinoma, which for a long time retain their shape.

It has been pointed out to me that the condition may be one of infection of the lymphatic channels and spaces in the wall of the thoracic duct; in that case one can only assume that the enlarged lymphatics leading from the primary seat of disease to the glands have had their walls infected in a similar manner. The absence of chylous ascites appears to point to the duct being pervious or to other channels being open. Troisier inclines to the latter view,—in fact, the former is not even considered.

The condition here recorded, then, is evidently a definite one, though at the same time rare. The cases present a remarkable similarity, not the least curious feature being the apparent union between the lining cells of the duct and the cells of the new growth.

December 2nd, 1902.

20. *The leucocytic changes following splenectomy combined with intra-venous injections of sodium cinnamate.*

By H. Batty Shaw.

(From the Pathological Laboratory, University College, London.)

The purpose of the experiments of which the present ones form part was to endeavour to find what share the spleen takes in the leucocytic changes produced under varying conditions of leucocytosis.

During the present year I have been able to show that when cats are injected with cinnamate of sodium, and leucocytosis results (1), an alteration of the relative proportion of leucocytes takes place (2). The change produced by the cinnamate of sodium in increasing the leucocytes of the blood does not appear to be due to an abstraction of fluid from the blood-vessels. The simpler lymphocytes appear to be transformed into polymorphonuclear cells, and also into intermediate forms. So far as the spleen is concerned it does not appear, judging from the results found in examining the blood of the splenic vein before and after injection with cinnamate of sodium, to aid or hinder this transformation.

In the present series of experiments fifteen animals (cats) were used. In only eight of these was there a leucocytosis, and deductions are drawn from these animals only, although in the remaining seven animals, despite the want of evidence of leucocytosis, similar relative changes were found in the percentage count of the various leucocytes.

The animals were anæsthetised with ether, and blood drawn from a branch of the right jugular vein, exposed by dissection, was subjected to numerical estimation. The red corpuscles were enumerated with the Thoma-Zeiss instruments, using Sir William Gowers' hæmocytometer fluid, and the white corpuscles were counted by using a ·2 per cent. solution of acetic acid and a Thoma-Zeiss apparatus. Films of blood were taken at the same time and stained by several methods, *e. g.* with Jenner's stain, with dahlia, and with the Ehrlich-Biondi-Heidenhain stain. The greatest sharpness of nuclear definition was, however, obtained with Leishman's stain (4).

The spleen was removed, and a quarter or half a gramme of cinnamate of sodium, dissolved in warm sterilised water, was injected by means of a hypodermic syringe into the jugular vein: with care the hypodermic needle could be removed, and the puncture in the vein allowed to close by clot without any loss of blood, nor was a ligature necessary after the injection of the salt. After an interval of two and three quarters to six hours the blood of the jugular vein was again examined, and comparisons were made with the results obtained before the splenectomy and injection of cinnamate of sodium.

Each animal was kept for at least twelve hours without food before the operations were performed.

Table I shows the details of the blood-count. Considerable variation will be found in the total numbers of red and white cells, and this may be accounted for by the difficulty in abstracting small amounts of blood, much more difficult than obtaining blood from the human finger or ear, for in this case the amount of escaped blood is very small. In the case of these experiments the vein was incised, and the points of the blood pipettes were held in the escaping stream, or the escaped blood was allowed to form a pool in the adjacent tissues, and then blood was immediately taken up into the pipettes from these collections. The variability in the white cells is to be regretted, for it has thus been necessary to make analysis of the various forms of white corpuscles from eight instead of fifteen animals.

Table II shows the analysis in percentages of all forms of leucocytes before and after experiment. It will be observed that in almost all cases, the exceptions being experiments Nos. 11 and 15, the *small lymphocytes are reduced* in number as a result of the experimental procedure, and also that in the majority of cases, thirteen out of fifteen, the *polymorphonuclear cells are increased,* the exceptions being Nos. 11 and 13.

From these results it seems justifiable to conclude that the blood enumerations shown in Table I are not to be relied upon, and that probably in all cases a leucocytosis has occurred as a result of the injection of cinnamate of sodium, because the other effect of injection of cinnamate of sodium, viz. the reduction of small lymphocytes and increase in polymorphonuclear cells, is present in the large majority of cases. However, as

TABLE I.—*Tabulated results of enumeration of red and white corpuscles before and after splenectomy combined with injection of cinnamate of sodium (fifteen animals). The figures represent the numbers per cubic millimetre of blood.*

Animal.	Amount of cinnamate of sodium injection.	Before combined splenectomy and injection.		After combined splenectomy and injection.			Result.
		Red.	White.	Red.	White.	Interval after splenectomy.	
1	¼ gramme	10,200,000	12,825	7,225,000	12,968	2¾ hours	Leucocytosis.
2	"	8,562,500	39,375	9,187,500	20,625	"	Leucopenia.
3[1]	"	10,887,500	14,112	6,375,000	12,343	3¼ hours	"
4 (control)	None	9,287,500	25,000	12,800,000	26,718	3 hours (after splenectomy)	Leucocytosis.
5	¼ gramme	10,362,500	24,530	11,337,500	37,810	5 hours	"
6	"	9,675,000	17,187	12,275,000	20,625	4¼ hours	"
7	"	14,625,000	14,530	13,650,000	13,750	3¾ hours	Leucopenia.
8	"	9,137,500	20,125	10,237,500	21,406	4½ hours	Leucocytosis.
9	"	8,175,000	14,062	6,337,500	15,312	5½ hours	"
10	"	8,437,500	17,812	8,512,500	16,562	5 hours	Leucopenia.
11	"	6,775,000	28,437	7,025,000	19,218	5¾ hours	"
12	"	10,600,000	20,000	12,025,000	36,875	6 hours	Leucocytosis.
13	"	9,787,500	15,781	7,825,000	11,562	3½ hours	Leucopenia.
14	½ gramme	12,875,000	8,331	12,750,000	14,062	5¾ hours	Leucocytosis.
15[2]	"	9,875,000	53,281	12,337,500	50,937	5½ hours	Leucopenia.

[1] Considerable hæmorrhage after splenectomy from slipping of a ligature.
[2] This animal had a large discharging abscess cavity in the back.

TABLE II.—*Tabulated results of effects of combined splenectomy and injection of cinnamate of sodium on fifteen animals.*

Animal.	Sex.	Weight in grms.	Before.							After.							Effect on total number of leucocytes.
			Small lymphocytes.	Large lymphocytes.	Transitional cells.	Immature polymorphonuclear.		Polymorphonuclear.	Coarse eosinophiles.	Small lymphocytes.	Large lymphocytes.	Transitional cells.	Immature polymorphonuclear.		Polymorphonuclear.	Coarse eosinophiles.	
						U.	O.						U.	O.			
1	M.	—	32	6	0	2	0	59	1	15	6	3	7	2	67	0	Leucocytosis.
2	M.	—	23	8	1	8	2	54	4	16	12	1	6	1	60	4	Leucopenia.
3	M.	—	36	8	0	5	0	47	4	35	7	0	1	1	53	3	"
4	M.	—	14	8	0	4	0	71	3	9	1	0	7	4	77	2	Leucocytosis.
5	M.	—	27	7	2	5	1	51	7	11	9	3	3	4	68	2	"
6	M.	—	34	5	0	3	1	52	5	12	5	5	2	0	75	1	"
7	M.	3530	31	6	1	2	4	53	3	3	4	1	3	3	86	0	Leucopenia.
8	F.	2950	37	4	5	1	2	46	5	12	2	3	4	1	73	5	Leucocytosis.
9	F.	2450	27	3	1	2	1	52	14	13	3	1	1	2	67	13	"
10	F. (preg.)	2820	30	4	3	0	2	56	5	21	7	4	3	1	58	6	Leucopenia.
11	F.	1437	29	10	0	2	1	53	5	38	2	5	0	0	49	6	"
12	F.	2140	33	9	3	1	1	43	10	4·5	2	5	2	1	85·5	0	Leucocytosis.
13	F.	2410	35	5	3	0	1	53	3	28	3	9	2	3	53	2	Leucopenia.
14	M.	2930	46	11	6	0	0	36	1	16	1	3	2	1	75	2	Leucocytosis.
15[1]	M.	2190	16	4	4	4	3	64	5	16	0	1	2	2	75	4	Leucopenia.
Averages			29·9	6·5	1·8	2·5	1·1	52·7	5·1	16·6	4·2	2·9	3	1·7	68·1	3·3	Leucocytosis—8 times. Leucopenia—7 times.

[1] This animal had a large discharging abscess cavity on the back.

splenectomy has also been performed, it is safer to exclude all cases in which leucocytosis was not demonstrated by the ordinary methods of counting.

Table III shows the effect in eight animals produced by the experiment in which leucocytosis was produced. As those cases alone are made use of which showed a leucocytosis, it is only necessary to refer to the *percentages* of the various forms of leucocytes, and not to the *absolute* counts. In every case the small lymphocytes were reduced in percentage; in four cases the large lymphocytes were also reduced, in three cases there was no alteration, and in one case there was an actual increase; the average of the results showed a reduction. The transitional cells were increased in four cases, unaltered in two, and reduced in two, and the average result was an increase. Under the heading of "immature" polymorphonuclear cells are included two forms of cells, the nuclei of which are intermediate in shape between the reniform nuclei of transitional cells and the complicated nuclei of the polymorphonuclear cells; in both cases the nucleus is like a strap free from indentations, and producing in different cases figures like the letters U and O. A special name has not been given to these cells, as they are apparently only more advanced stages of the transitional cells; the only reason for their separate enumeration is that the shape of the nucleus has been made the great criterion for distinguishing what appears to be varying degrees of development of one and the same corpuscle, viz. the small lymphocytes into the several varieties of cells met with in the circulation. In five cases there was an increase in the number of U cells, and in three a decrease; in five cases the O cells were increased; in two they were unaltered; in one they were reduced in number. In both cases the average result was an increase.

With respect to the polymorphonuclear cells there was an increase in every case, just as in every case there was a reduction of both varieties of lymphocytes.

Contrasting the condition of the blood before and after the experiments, it would seem that taking the small lymphocytes and the polymorphonuclear cells as extremes of a series of cells, the former being of much lower differentiation than the latter, as a result of the experiments performed the simpler lymphocytes have been *reduced* in number and the polymorphonuclear

TABLE III.—*Comparison Table to show the changes in relative proportions of various white corpuscles in jugular blood removed before and after splenectomy combined with injection of cinnamate of sodium in eight animals in which leucocytosis was observed. The figures represent percentages.*

Animal.	Small lymphocytes.		Large lymphocytes.		Transitional cells.		Immature polymorphonuclear cells.				Polymorphonuclear cells.		Coarse eosinophiles.	
							U.		O.					
	Before.	After.	Before.	After.	Before.	After.	Before.	After.	Before.	After.	Before.	After.	Before.	After.
1	32	15	6	6	0	3	2	7	0	2	59	67	1	0
4	14	9	8	1	0	0	4	7	0	4	71	77	3	2
5	27	11	7	9	2	3	5	3	1	4	51	68	7	2
6	34	12	5	5	0	5	3	2	1	0	52	75	5	1
8	37	12	4	2	5	3	1	4	2	1	46	73	5	5
9	27	13	3	3	1	1	2	1	1	2	52	67	14	13
13	33	4·5	9	2	3	5	1	2	1	1	43	85·5	10	0
15	46	16	11	1	6	3	0	2	0	1	36	75	1	2
Aver'ge	31·25	11·59	6·63	3·62	2·12	2·87	2·25	3·50	·75	1·87	51·25	73·43	5·75	3·12

cells *increased*, and that there has also been in the majority of cases an increase of the transitional and immature polymorphonuclear cells; that the changes are constant in the extremes of the series, and are generally progressive in the case of the intermediate cells, and appear to be quite in harmony with the view that lymphocytes give origin to the other white blood-corpuscles, possibly in the blood-stream, possibly in passing through such structures as bone marrow, as shown by von Roietzky's observations (3).

As to the coarse eosinophile cells, Table III shows that in six cases they were reduced, in one unaltered, and in one increased in number. Possibly these cells are derived from the polymorphonuclear cells, and represent a less active form—an involution, and that the short time the animals were under ether may not have been sufficient to allow the onset of this change, so that with the general increase of the other leucocytes they are reduced relatively.

Table IV shows an analysis of all the experiments carried out in this connection. It would appear that the administration of ether for two and a half hours merely stimulated the lymphocytes to produce an increase of the transitional and immature polymorphonuclear cells without increasing the polymorphonuclear cells. Splenectomy and administration of ether for three hours produces a more definite effect, but nothing very exceptional; indeed, the difference in the two cases might be quite independent of splenectomy, and be accounted for by the increased duration of the administration of ether.

The injection of cinnamate of sodium, however, produces still more definite results of the same order, but somewhat less in degree than those produced by splenectomy combined with injections of sodium cinnamate.

Conclusions.—In *résumé* this series of experiments tends to confirm the view that the more complex leucocytes are derived from the simpler ones. Further, that the only immediate difference, *i. e.* difference produced within a few hours by the removal of the spleen, combined with the injection of cinnamate of soda, is to intensify the final conversion of intermediate cells to polymorphonuclear cells, a change already shown to have resulted from the mere injection of cinnamate of sodium.

TABLE IV.—*Résumé of leucocytic change in jugular blood before and after various conditions of experiment.*

Nature of experiment.	Small lymphocytes.		Large lymphocytes.		Transitional cells.		Immature polymorphonuclear cells.				Polymorphonuclear cells.		Coarse eosinophile cells.	
							U.		O.					
	Before.	After.	Before.	After.	Before.	After.	Before.	After.	Before.	After.	Before.	After.	Before.	After.
Anæsthetisation with ether for 2½ hours . . . . . One animal.	24·00	17·50	7·50	4·00	0·00	0·50	10·00	21·50	3·50	4·50	53·00	51·50	2·00	0·50
Splenectomy 3 hours after . . One animal.	14·00	9·00	8·00	1·00	0·00	0 00	4·00	7·00	0·00	0·40	71·00	77·00	3·00	2·00
Injection of cinnamate of sodium. Average result . . . . Five animals.	25·00	14·80	4·10	4·12	0·70	1·40	10·90	10 32	2·00	3·02	54·80	64·52	2·50	1 82
Splenectomy combined with injection of cinnamate of sodium for 2¾ hours, 6 hours later. Average result . . . . . Eight animals.	31·25	11·59	6·63	3·62	2·12	2·87	2·25	3·50	0·75	1·87	51·25	73·43	5·75	3·12

REFERENCES.

1. *Richter and Spiro.*—'Arch. f. exper. Path. u. Pharmakol.,' Leipzig, 1894, Bd. xxxiv, S. 289.
2. 'Journal of Pathology and Bacteriology,' March, 1902.
3. *Von Roietsky, quoted by Ehrlich and Lazarus.*—'Histology of the Blood,' edited by W. Myers, Cambridge, 1900.
4. *Leishman.*—'British Medical Journal,' 1901, pp. 635 and 757.

December 16*th*, 1902.

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21. *The morbid anatomy of erythromelalgia.*

By H. BATTY SHAW.

(From the Pathological Laboratory, University College, London.)

ERYTHROMELALGIA is the name given by Weir Mitchell (1) to a condition of the extremities in which redness and pain are associated. Sir Thomas Barlow (2), in contrasting the disease with Raynaud's disease, summarises the differences thus:—Dependence produces considerable increase of the dusky red or violaceous tint of the extremity affected; the arteries in this position of the limb may pulsate forcibly; pain is common, sometimes constant, and more especially when the limb is dependent or the parts pressed upon; in wintry weather, or on the application of cold, the conditions are relieved; on the other hand, warmth and summer weather increase the pain; there is no loss of sensation, but there may be increased sensitiveness; the local temperature of the affected parts may be raised or lowered; gangrene does not occur; the affection is asymmetrical; there is a certain amount of swelling, sometimes allowing pitting on pressure, sometimes not; incisions over such swelling, even down to the bone, have proved useless; excessive pain on pressure upon the nerves supplying the parts affected is not found; muscular wasting is found, but explainable by the disuse of the limb, and is not at all as severe as in cases of disease of the peripheral nerves; a reaction of degeneration in the nerves of the affected parts has not been found; the deep reflexes, with few exceptions, are not reduced. The disease may

occur alone, or may be associated with other grave disturbances of the central nervous system; for example, hemiplegia, general paralysis, tabes dorsalis, myxœdema, disseminated sclerosis, and chronic myelitis (3).

Cases occur which are somewhat similar to the cases described by Weir Mitchell, but which point to a relationship with such diseases as Raynaud's disease and sclerodermia; and Cassirer (4), in a recent monograph, has endeavoured to draw clinical distinctions between these three maladies and the affections intermediate between them.

The three cases examined and reported upon in this communication were typical ones of erythromelalgia. The pain was so severe and the affected extremity so useless that amputation was performed.

Method of investigation.—The affected parts, after removal, were hardened in alcohol (Case 1 and Case 2) or in Müller's fluid (Case 3). Sections were made of the soft tissues of each digit, the phalanges being resected from the periosteum; in the case of the foot (Case 1) the sections made were representative of the whole length of the digit, including the ends of the toes; in the other two cases a ring of tissue was examined, the length of which, measured along the axis of the digit, was about half an inch. The sections were cut in paraffin for the study of the vessels, and in celloidin for that of the nerves. In order to detect any recent nerve degenerations the nerves were stained by a combination of Busch, Benda and van Gieson's methods, and in some cases by Marchi's method. In addition, portions of the larger vessels and nerves of the parts affected were dissected from the adjacent tissues, mounted as above, and cut transversely and longitudinally, and subjected to the same method of staining. The special points investigated have been—(1) arterial and venous changes; (2) changes in the nerves, especially the finer terminal branches, with respect both to a replacement of nerve-fibres by fibrous tissue, and also to recent changes degenerative in character. In estimating the possible vascular and nervous changes, constant reference was made to sections prepared from the digits of the foot of patients of a similar age dying from some malady not likely to cause peripheral, vascular, and nervous disease,—for example, death from perforation of a gastric ulcer in a young woman.

CASE 1.—A. K—, a young woman aged 24 years, was admitted to University College Hospital under Dr. Charlton Bastian's care; subsequently she was admitted to St. Bartholomew's Hospital at Rochester, and amputation was performed for extreme pain. This patient had suffered from her symptoms for five years. The left foot would become reddish blue, especially when held dependent or when it was kept warm; there was also some puffiness and hyperæsthesia. There were brief periods when the foot in parts became doubtfully slightly anæsthetic, but such anæsthesia was never permanent. There were also nutritional disturbances of the nails and skin; there

FIG. 15.

FIG. 16.

FIG. 15.—Transverse section of the external plantar artery of Case 1, showing irregular thickening of the internal coat, and at one part doubling of the elastic lamina of Henle.

FIG. 16.—Transverse section of the external plantar vein of Case 1, showing almost complete occlusion of the lumen by thrombosis and also well-marked canalisation.

was no reaction of degeneration. The plantar reflex was absent in this foot, and very feeble in the right foot; the knee-jerks were brisk; there was some tenderness in the calf muscles. When the foot was placed in warm water patches of salmon-red colour appeared in the midst of the general blueness of the extremity.

Morbid anatomy.—(*a*) *Vessels.*—Some thickening in the intima was present in all the digital arteries, and in those of the third toe it was considerable. Irregularly disposed thickening was also present in the internal and external plantar arteries,

especially in the latter. The most pronounced changes were met with in the venæ comites of these vessels. The lumen of the veins accompanying the external plantar artery was almost quite occluded by clot, and marked canalisation was present. The dorsal artery and veins were normal.

(*b*) *Nerves.*—In no case of a digital or plantar nerve was any recent degeneration discovered. Abundant nerve-fibres were seen in the case of the digital nerves distributed to each toe except in the case of the great and second toe, in which the nerve-fibrils were very much scattered instead of being collected into coarse bundles; in no case, however, were bundles of fibrous tissue found containing less than a dozen nerve-fibres. The plantar and musculo-cutaneous nerves were quite healthy.

Case 2 (5).—P. N—, a pointsman aged 29 years, was admitted to University College Hospital under Dr. Bradford's care. Ten years previous to the onset of his symptoms he had been struck on the back of the left wrist; an abscess developed and slowly healed. Nothing abnormal was noticed till three years before he came under Dr. Bradford's care. As in Case 1, the affected hand became blue, and was mottled with salmon-red coloured areas; there was pain, increased by warmth, œdema which pitted, and there were nutritional disorders of the skin and nails; the former was quite glossy, and the latter more opaque than natural, and showed transverse ridges. Sensation was perfect in every digit, and in all parts of the hand, wrist, and forearm; there was no hyperalgesia; there was no reaction of degeneration.

Morbid anatomy.—(*a*) *Vessels.*—The digital arteries and veins of the thumb alone showed extensive thickening of the intima; the arteries of the index finger showed less but obvious thickening of the intima, whereas in the digital vessels of the rest of the fingers the changes in the intima were very slight. Some intimal thickening was visible in the ulnar artery, the deep palmar arch, and in the comes nervi mediani; in these vessels, and in the radial artery, the elastic lamina of Henle was very deficient.

(*b*) *Nerves.*—There was no trace of recent degeneration in any of the nerves—digital, radial, median, or ulnar,—except in the digital nerves of the index finger, in which some nerves and

some nerve-endings in the skin showed staining attributable to the osmic acid. This was probably an artefact, and due to the fact that the amputated hand had been hardened in alcohol. There was no fragmentation whatever of the medullary sheaths.

FIG. 17.

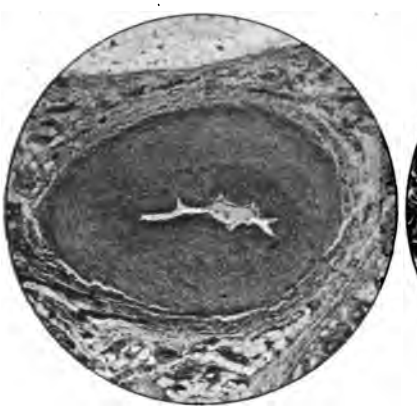

FIG. 18.

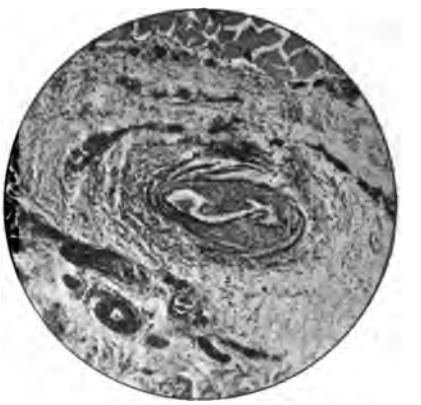

FIG. 17.—Transverse section of one of the digital arteries of the thumb of Case 2, showing great narrowing of the lumen of the vessel and marked increase of the internal coat. The elastic lamina represented by small areas of homogeneous material, is either very much fenestrated or deficient.

FIG. 18.—Transverse section of one of the digital veins of the thumb of Case 2, showing the internal coat encroaching in irregular masses upon the lumen of the vessel.

CASE 3.—E. B—, a young woman aged about 20 years, came under the care of Sir Thomas Barlow. Previous to her admission to University College Hospital she had had symptoms for eighteen months following a slight injury to the right hand. This injury was immediately succeeded by swelling, inflammation, and aching pain. She was treated at various institutions, and in one the affected hand was incised and scraped, but with no benefit. The hand continued to be very painful; occasionally the arm throbbed from the fingers to the elbow; sometimes it felt hot, at others it was very cold; passive movement of the hand was possible but painful; there was puffiness of the dorsum of the hand and of the fingers, the nails were ribbed, and the skin was thin and somewhat polished; pressure caused pitting of the subcutaneous tissues; there were areas of localised tenderness and blotches of purple coloured skin; there was no anæsthesia; the pain was of a "tingling" character;

the nerve-trunks were not tender. At the time of the amputation it was thought that some of the vessels (anterior interosseous) bled less than usual.

Morbid anatomy.—(*a*) *Vessels.*—The digital arteries of the fingers showed very slight thickening, those of the thumb showed obvious thickening in the internal coat. The ulnar artery showed some thickening of the internal coat, but the radial artery showed much more pronounced changes.

(*b*) *Nerves.*—There was no definite sign of recent degeneration in any of the nerves, nor was there an apparent deficiency of nerve-fibres or increase of fibrous tissue in the larger nerve-trunks or in the digital nerves.

FIG. 19.

Transverse section of the ulnar artery of Case 3, showing irregular thickening of the internal coat.

No syphilitic history could be obtained in any of the above cases, nor were there any symptoms or signs of central nervous disease.

I should like to include in this analysis the report of a case by Dr. F. Parkes Weber (12), which he has called an "anomalous and asymmetrical case of sclerodactylia with Raynaud's phenomena." Dr. Parkes Weber is not inclined to consider the case one of erythromelalgia, and therefore I do not include it in the analysis. However, it has much in common with several of these nine cases, and I am the more wishful to call attention to the case, as the morbid anatomy of the vessels and nerves has been investigated.

A patient, A. B—, aged 25, a waiter, had considerable wasting and contraction of the muscles of the left leg; the skin of the left foot was tense, shiny, and livid, and decidedly cold to the touch; the colour sometimes was dark purple, almost black. When the foot was made warm he suffered from pain in the foot; there was pain also when the foot was cold; dependency did not produce pain. There was an ulcer of the great toe, the fourth and fifth toes were wanting; the nail on the great toe was absent, and those of the two remaining toes were quite horny; there was a scar on the heel; the right foot (except for some scars, purpuric spots, and some pigmentation) was healthy. Both knee-jerks were present; there was no reaction of degeneration, and the anterior and post-tibial arteries pulsated in both limbs. There were no abnormalities of sensation.

Amputation was subsequently performed. Examination of the internal plantar and dorsal arteries showed decided thickening of the middle coat, but no endarteritis obliterans or thrombosis; also some thickening of the intra-muscular arterioles was noticed. Dr. F. E. Batten examined the nerves and found they were quite normal. Dr. Parkes Weber looked upon the case as one of "idiopathic obliterative arteritis." There were, however, so many symptoms common to this case and those reported in this communication that it is possible to group them together, more particularly as the microscopic evidence in all cases points to vascular change.

Of the nine cases of erythromelalgia which have been subjected to examination, one case (Weir Mitchell and Spiller, 8) showed what appeared to be a reduction of the number of nerve-fibres in a portion of nerve excised, with an increase of fibrous tissue; there was, however, no anæsthesia in those parts to which the nerve was distributed; there were changes in the arteries. In another case (Auerbach, 10) there was degeneration of certain posterior nerve-roots, but the peripheral nerves were quite healthy. (No mention is made of the morbid anatomy of the vessels in this case.) In Weir Mitchell's first case (6) the nerves showed no change, but changes were present in the arteries; in his second case (7) the nerves removed were quite healthy. Dehio's case (9) showed narrowing of the lumen of the artery, with thickening of the intima, and no changes were found in the ulnar nerve. In

Sachs and Wiener's case the vascular changes were probably primary, and the increase of fibrous tissue in the nerve-trunks secondary.

In the cases reported in this communication vascular change was present in all (least in Case 3). Such change was mostly an increase in the intima of the arteries, and occasionally thrombosis and changes in the inner coat of the veins. The nerves were investigated even to their terminations, and no degeneration was found, nor was there any suggestion of increase of fibrous tissue in the trunk of the nerves.

Dr. Parkes Weber's case, even though it is not called erythromelalgia, at any rate affords proof that many of the leading symptoms, so like those of erythromelalgia, are associated with vascular changes, the nerves being quite normal.

In no case has recent degeneration of nerve-fibres been demonstrated, and in not one of the nine cases analysed was anæsthesia ever present. As a result of a consideration of these reported cases, it would appear that erythromelalgia, when occurring independently of central nervous change, is associated with but one morbid picture, that of local vascular change.

I desire to express my gratitude to my colleagues for permission to make use of the clinical reports and the material of their cases, and to Mr. Sherstone Baker for sending for examination the foot amputated in Case 1.

REFERENCES.

1. *Weir Mitchell.*—'American Journal of the Medical Sciences,' July, 1878, p. 17.
2. *Allbutt.*—'System of Medicine,' 1899, vol. vi, pp. 607—621.
3. Also references to Henoch, Machol, Landgraf, Henry, Edinger, Woodnut, and James Collier.
4. *Cassirer.*—'Die vasomotorisch-trophischen Neurosen,' Berlin, 1901, S. 555 et seq.
5. 'Transactions of the Clinical Society,' London, 1900, p. 223.
6. *Weir Mitchell.*—'Clinical Lessons on Nervous Disease,' Philadelphia, 1897, Case 59, p. 107.
7. Ditto, Case 58, p. 185.
8. *Weir Mitchell and Spiller.*—'Amer. Journ. of Med. Sciences,' Jan., 1899, p. 1.
9. *Dehio.*—'Berl. klin. Woch.,' 1896, No. 37, S. 817.
10. *Auerbach.*—'Deut. Zeit. f. Nervenheilk.,' 1897, xi, S. 142.
11. *Sachs and Wiener.*—'Deut. Zeit. f. Nervenheilk., 1899, xv, S. 286.
12. *F. Parkes Weber.*—'British Journal of Dermatology,' February, 1901, p. 41, and October, 1902, p. 388.

November 18th, 1902.

Synopsis of Symptoms, etc., and Morbid Anatomy

Author.	Sex.	Age.	Pain.	Redness.	Swelling.	"Trophic" change.	Muscular weakness.
Weir Mitchell (6)	M.	48	Pain in right foot	Yes	—	—	—
Weir Mitchell (7)	M.	21	Pain present in first and second toes of right foot	Yes, in first and second toes	Yes	Atrophy of muscles of leg	Slight tremor; spasm occasionally; no paralysis
Weir Mitchell and Spiller (8)	M.	61	Right foot worse with warmth	Yes	No	—	Normal
Dehio (9)	F.	50	Pain in left hand and foot, especially with movement; paroxysmal	Affected part blue	—	Atrophy of the skin of fingers	—
Auerbach (10)	M.	46	Right and left legs and feet	Yes; increased by depression of limbs	Yes; right foot and leg, especially when dependent	Ridging of nails	—
Sachs and Wiener (11)	M.	36	Yes, left foot	Yes	Yes	Yes; skin dry and smooth	Some wasting of peroneus and of whole limb ultimately
Case 1 of this contribution	F.	25	Yes, left foot	No	Yes	Yes, skin and nails	Yes
Case 2 of this contribution	M.	29	Yes, left hand	Yes	Yes	Yes, skin and nails	Yes
Case 3 of this contribution	F.	Abt. 20	Yes, right hand	Yes	Yes	Yes, skin and nails	Yes

of Nine Reported Cases of Erythromelalgia.

Sensory disturbance.	Pulse.	Tenderness in nerve-trunks.	Morbid anatomy.	Remarks.
Hyperæsthesia	Arterial pulsations present	No trace of tenderness	Nerve showed no change; arteries and arterioles showed increase of the middle coat and calcification	Nerves excised for remedial purposes.
General hyperæsthesia	Visible arterial pulsation	Only once after keeping limb raised (p. 189)	The musculo-cutaneous nerve and branches of the internal saphenous nerve were quite healthy; arteries not operated upon	History of previous injury from a falling stone.
Normal in both feet	Lost in whole limb from groin downwards	No tenderness along course of nerve-trunks	Apparent reduction of nerve-fibres of great toe and increase of fibrous tissue; vessels much diseased (especially intima and media of arteries)	Amputation.
Hyperæsthesia and hyperalgesia	Vessels showed arteriosclerosis	—	Ulnar nerve normal; thickening of intima of ulnar artery and narrowing of lumen	Excision for remedial purposes.
Sensibility to touch, heat, and cold normal	—	—	P.M.—Peripheral nerves normal; cells of ganglia in posterior nerve-roots also normal; degeneration of root-bundles in cord; no mention made of peripheral arteries	Patient had had syphilis.
—	Active pulsation of the arteries of the foot	—	Anterior tibial artery and popliteal artery thrombosed; veins thickened; nerve changes slight and secondary; some increase of connective tissue	Erythromelalgia followed by gangrene.
Hyperæsthesia; no anæsthesia	Arteries of dorsum of foot felt pulsating	None	Thickening of intima of arteries; thrombosis of veins; no change in nerves	Amputation for pain.
Sensation normal; no hyperæsthesia	Pulsation of vessels obscured by œdema	None	Thickening of intima of arteries; no change in the nerves	Symptoms followed 3 years after an injury; amputation for pain.
No anæsthesia	Pulse good and equal to that of left hand; vessels not thickened clinically	None	Thickening of intima, especially of radial artery and digital arteries of the thumb; no change in the nerves	Symptoms followed an injury to the hand.

22. *Case of chronic indurative mediastino-pericarditis producing stenosis of the superior vena cava, etc.*

By T. W. P. Lawrence and H. Batty Shaw.

The patient, E. P—, was a clerk aged 36 years. Fifteen years ago he contracted syphilis, giving a history of an initial lesion followed by a cutaneous eruption. Five years ago he began to suffer from palpitation, dizziness, and faintness; he was also weak, short of breath, was troubled with cough, and spat blood; after every meal he was sick. He was treated privately, and at the Royal Free Hospital as an out-patient for some ten weeks. He was admitted later as an in-patient at the Mount Vernon Consumption Hospital (July, 1898). He was still suffering from shortness of breath and slight hæmoptysis. No very definite signs were found in the lungs, and the evening temperature was found to be about 100°. After six weeks he was discharged improved and was able to resume work. Three and a half years ago he was readmitted to the Mount Vernon Hospital with hæmoptysis and a return of the symptoms mentioned above. The apex-beat was found to be displaced outwards about an inch; enlarged veins had developed on the front of the chest and abdomen, and there was cyanosis of the neck and face. Shortly after admission thirty-six ounces of blood-stained serous fluid were removed from the right pleural cavity. The sputum was found to be free from tubercle bacilli, but contained diplococci, staphylococci, and streptococci. One month later dulness was present at the base posteriorly of the right side of the chest, and this was continuous with dulness in the abdomen reaching one or two inches below the right costal margin. In the mornings the face, neck, and eyelids were puffy, but towards evening these signs disappeared; the pulses are said to have been unequal, but the pupils were quite equal in size. One month later the dull area in the chest had increased, but aspiration was not again performed. Shortly after, in the beginning of the year 1900, he was discharged, puffiness and cyanosis of the face being still present; the veins of the front of the chest and abdomen were enlarged and very tortuous,

and the girth of the right half of the chest was one and three-quarter inches greater than that of the left. A stay of one month at Ambleside was followed by considerable improvement, and he continued his attendance at the Royal Free Hospital, at which institution he was treated with potassium iodide.

For the next one and a half years, that is till June, 1902, he was still ailing and unable to go to work. At this date, however, he resumed some light duties at the office where he was engaged; he was unable at this time to lace his boots, became very blue when he bent forward to wash himself, was constantly sick after meals, and rested at night propped up against pillows. He was admitted to University College Hospital on December 8th, 1902, under Dr. Bradford's care. The eyelids were very puffy and the neck swollen. The veins of the neck were very much enlarged, and so tightly distended as to give the feeling of enlarged glands. The apex-beat of the heart was displaced, and there were signs of fluid at the right base. The veins of the front of the chest and abdomen were greatly enlarged and filled from above. There was some dulness below the right costal margin, but the liver and spleen were not felt. There was some twitching of the left side of the face, pain in the right side of the chest, and the temperature was 100·2°. There was no œdema of the lower extremities or abdominal walls, nor ascites till latterly. The right half of the chest was aspirated, and six ounces of turbid blood-stained fluid were drawn off. The pulses, though rather small, were equal, quite regular, and the tension was well maintained. Coughing was followed by a sensation of faintness. A few days before death there was general œdema of the whole body, and the patient became delirious. Death occurred on December 30th, 1902.

Post-mortem.—Thin purulent fluid was found in the right pleural cavity.

Examination of the viscera of the chest.

1. *Heart and pericardium.*—The right orifice of the transverse sinus of the pericardium is closed by adhesions, the convexity of the ascending part of the aorta being united to the right auricle and to the commencement of the vena cava superior. The left orifice of the sinus is open, but the lumen of

the sinus at some little distance from the orifice is closed by adhesions. On cutting through the adhesions a cavity is opened which corresponds in position to the right half of the transverse sinus. The cavity measures 3·5 cm. in the vertical and transverse directions, and rather less than 2 cm. in the antero-posterior direction. Its wall is thick and rigid, being composed of dense fibrous tissue; its inner surface is of a dull red colour, and is coated with a layer of loosely adherent inflammatory exudation, having the microscopic characters of a purely fibrinous deposit. The wall of the cavity is adherent in front to the hinder wall of the first part of the aorta, behind to the anterior wall of the left auricle, and on the right to the inner wall of the right auricle and the commencement of the superior vena cava; the right branch of the pulmonary artery crosses its upper part. These structures which surround the wall of the cavity are indurated in varying degrees. The aorta is but slightly affected, the walls of the two posterior sinuses of Valsalva showing some signs of chronic endarteritis, and a slight puckering being present in the wall of the right posterior sinus. The anterior wall of the left auricle is considerably thickened, and the induration has extended into the anterior and upper part of the septum auricularum and around the orifice of the right pulmonary vein, there being but one vessel opening into the right side of the auricle. By the contraction of the indurated tissue the orifice of the right pulmonary vein has become almost obliterated, and measures less than 2 mm. in diameter; the vein itself is not diminished in calibre, nor is its wall thickened, the stenosis being limited to the orifice. The inner wall of the right auricle is converted into dense fibrous tissue, which has a scar-like appearance and greyish-white colour, and presents numerous patches and streaks of grey pigmentation. The induration extends into the anterior and upper part of the septum auricularum, and involves in less degree the floor of the fossa ovalis; it also extends upwards around the orifice of the superior vena cava, which is almost obliterated, its diameter measuring 2 mm. The commencement of the superior vena cava, from its lower end to the orifice of the vena azygos major, is adherent to the aorta, to the right division of the pulmonary artery, and to the lower of the two primary divisions of the right bronchus, and it is surrounded by

deeply pigmented and indurated tissue, by which it is greatly constricted. The constriction commences abruptly immediately below the orifice of the vena azygos major, the circumference of the vessel, at this level, measured on the inner surface of the opened vein, being 13 mm. From this level downwards the diminution in calibre gradually increases till the vessel is reduced, as before stated, to a diameter of 2 mm. at its termination in the auricle. Within the constricted portion of the vein a fold of the inner coat of the vessel is present, produced apparently in the process of contraction, and having the usual semilunar form of a venous valve; the fold is, however, disposed with its free edge directed upwards, and its effect, if any, on the blood-stream would have been to oppose the return of blood towards the heart. There is no venous thrombosis. The right branch of the pulmonary artery is not appreciably diminished in calibre or otherwise affected.

From around the origin of the vena cava superior the induration extends downwards, on the exterior of the heart, along the line of pericardial reflection which crosses the root of the right pulmonary vein, and below this along the line of reflection of the pericardium on the posterior surface of the right auricle, where a dense fibrous band, 1·5 cm. in width, is present, uniting the auricle to the wall of the pleuritic cavity to be subsequently mentioned. The parietal and visceral layers of the pericardium are adherent for a few millimetres from the line of pericardial reflection mentioned, and also above this where the line crosses the vena cava superior. The induration is slight on the left side of the right pulmonary vein, which, as before stated, is not constricted except at its orifice, and it does not extend on to the hinder surface of the left auricle nor around the left pulmonary veins.

Parts of the right and posterior surfaces of the parietal pericardium are adherent to the mesial surface of the right lung and to the wall of the pleuritic cavity mentioned below; here the pericardium is thickened. In all respects other than those above detailed the heart and pericardium are normal.

The right and left innominate veins and the upper part of the vena cava superior measure 4 cm., 2·5 cm., and 4·2 cm. in circumference respectively; the vena azygos major measures 2·6 cm. in circumference at its termination, these measurements

being taken on the vessels in the undistended condition. The appearance of these vessels is normal.

2. *Lungs and mediastinum.*—The base and lower two thirds of the postero-external surface of the right lung are coated with a thick fibrous layer, which formed part of the wall of a pleuritic cavity. The surface of this layer is uneven, and in a

FIG. 20.

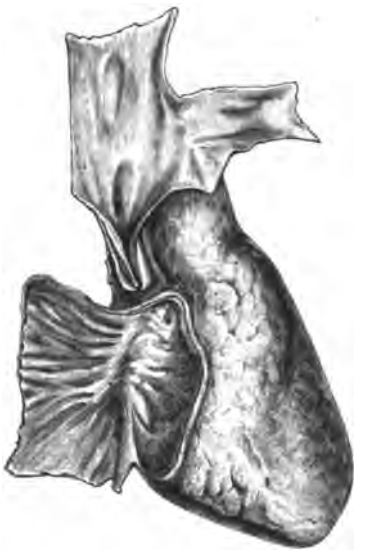

FIG. 21.

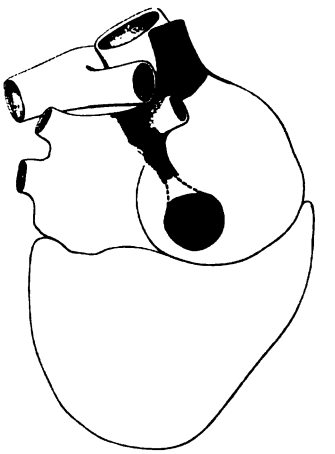

FIG. 20.—The heart seen from the right side. The right auricle has been opened to show the thickening and contraction of the inner wall and the associated stenosis of the orifice of the superior vena cava. The superior vena cava has been opened to show its constriction from the orifice of the vena azygos major downwards. (From a drawing by Mr. T. W. P. Lawrence.)

FIG. 21.—A diagram of the postero-inferior aspect of the heart. The black shading indicates the position of the indurated tissue, on the exterior of the heart, at the origins of the superior vena cava and the right pulmonary vein, and along the line of pericardial reflection on the posterior surface of the right auricle. (From a drawing by Mr. T. W. P. Lawrence.)

few places covered with patches of inflammatory exudation. From the inner margin of the base of the lung, which is pressed up considerably above its normal level, the wall of the pleuritic cavity is prolonged downwards, and is in this part in contact with and adherent to the pericardium and the hinder wall of the right auricle along the line of pericardial reflection. The

apex of the lung and its antero-external surface were closely adherent to the chest wall; the inner surface of the lung is adherent to the mediastinal pleura and to the pericardium. On section the lung exhibits pneumonic consolidation and collapse; but caseation, fibroid induration, and cavities are absent.

The left lung is normal. The bronchi and their primary branches are normal. The lymphatic glands above the right bronchus and extending into the tissues of the lower part of the neck are enlarged, but none of the glands of the chest present caseation or calcification. The areolar tissue of the mediastinum is normal except where it is in relation with the pulmonary adhesions and the induration around the great veins above described; in these situations it is indurated.

We are indebted to Dr. J. Rose Bradford for the notes of this case whilst under treatment at University College Hospital, and to Dr. S. R. Williams, resident medical registrar and pathologist to the Mount Vernon Hospital, for an account of the patient's illness whilst under treatment at that hospital.

REFERENCES TO REPORTS OF SIMILAR CASES, IN WHICH STENOSIS OR OCCLUSION OF THE SUPERIOR VENA CAVA OCCURRED AS A RESULT OF INDURATIVE MEDIASTINO-PERICARDITIS.

1. *Habershon, S. O.*—'Trans. Path. Soc. of London,' 1876, vol. xxvii, p. 79.
2. *Widenmann.—Vide Kussmaul.*—'Berlin. klin. Wochenschr.,' 1873, S. 433, 447, 461.
3. *Kussmaul.*—Ibid., 1873, S. 447.
4. *Cantilena, quoted by Hare.*—'Mediastinal Disease,' Philadelphia, 1889, p. 95.
5. *Hutton.*—'St. Thomas's Hospital Reports,' New Series, vol. xiii, 1883, p. 211.
6. *Sir Dyce Duckworth and Dr. A. E. Garrod.*—'St. Bartholomew's Hospital Reports,' 1896, vol. xxxii, p. 71.
7. *Green, T. Henry.*—'Trans. Path. Soc. of London,' 1876, vol. xxvii, p. 118.
8. *Bennett.*—'Dublin Journal of Medical Science,' 1875 (quoted in reference No. 6).
9. *Meigs.*—'Transactions College of Physicians,' Philadelphia, 1886, vol. viii, p. 13.
10. *Werner.*—'Beitrag zur Lehre von den mediastinal Geschwülsten,' Dissert., Berlin, 1892; quoted by Hoffmann, Nothnagel's 'Spec. Path. u. Therapie,' vol. xiii, S. 84.
11. *Duchek.*—'Vierteljahresschr. f. d. prakt. Heilk.,' Prague, 1854, Jahrg. 11, Bd. i, S. 109.
12. *Eppinger.*—'Prager med. Wochenschr.,' 1876 (No. 39, quoted in reference No. 13).

13. *Schrötter.*—Nothnagel's 'Spec. Path. u. Therapie,' vol. xv, Th. 2, S. 488.
14. *F. T. Roberts.*—Allbutt's 'System of Medicine,' London, 1899, vol. vi, p. 81.

Some of the above references have been obtained from a monograph by Dr. Thomas Harris on 'Indurative Mediastino-pericarditis,' London, 1895, p. 65 (reprinted from the 'Medical Chronicle,' 1894–5).

February 17*th*, 1903.

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23. *Ehrlich's dimethyl(p)-amidobenzaldehyde reaction.*

By H. W. Armit.

At the kind invitation of Geh. Ehrlich I have studied the clinical aspects of an aldehyde colour reaction, and propose dealing with the results of my observations on it. Before entering into the subject I have to express my indebtedness to Dr. P. Horton Smith, Dr. E. W. Goodall, Dr. Sykes, Dr. Quosig, and others, who have kindly allowed me to use their clinical material, and Drs. Dean and Todd for their courteous help in performing some animal experiments for me.

The chemistry of the body and its fluids is unfortunately very obscure, and only a small number of the normal constituents are known to us at present. These constituents are recognisable either because they exist in considerable quantity or because they are characterised by peculiar chemical reactions. In order to gain some knowledge of other compounds, Ehrlich [1] sought to produce combinations in the form of colour-bodies, and although he states that the discovery of hitherto unknown bodies is largely a matter of chance, he has set to work from a sound chemical basis. Two large chemical groups exist, which are capable of anchoring other complexes to form colour-bodies, viz. the diazo and the aldehyde. I do not propose to enter into the subject of the former to-day. The latter combination depends on a peculiar group arrangement, which takes the form of a double binding. If aniline (amidobenzoin) be added to benzaldehyde a new body is formed, benzyliden-aniline, and water is liberated. The formula of this body is—

$$C_6H_5C = NC_6H_5,$$

and the double binding between the C and N is spoken of as a

[1] *Ehrlich,* 'Die medic. Woch.,' April 15th, 1901.

chromophoric complex, or the azomethin group. The tinctorial characters of the group are not well marked, and the body benzyliden-aniline has only a weak yellow colour. If one substitutes a benzaldehyde, which contains an amido group capable of binding an acid in the para position, one obtains intense tinctorial characters, and the complex is then termed auxochrom. The coloration becomes deeper yet if one uses a dimethyl derivative of the para-amido-benzaldehyde. The reagent which Professor Ehrlich kindly put at my disposal is this derivative, and has the formula

$$C_6H_4 - CHO^{(1)} - N(CH_3)^{(4)}_2.$$

Dimethyl-para-amido-benzaldehyde is a crystalline whitish substance, which is soluble in acids, chloroform, ether, and insoluble in water and alkaline solutions. If one adds weak acid solutions of certain aromatic bases, deeply coloured and mostly insoluble bodies are formed, which are known as azomethin dyes. The urine contains a substance in solution which anchors dimethyl-benzaldehyde to form a cherry-red colour-body; this takes place to a greater or less extent in normal urines, but in some pathological conditions the reaction is most striking. Proescher[1] has analysed this combination, and found that the red body, which he isolated only in small quantities, has the empirical formula approximately of $C_{16}H_{24}O_6N_2$, which would give the formula of the unknown substance in the urine, after subtraction of dimethyl, $-O + 2H_2O$, as $C_7H_{15}O_6N$. The nearest known body is glucosamine, $C_6H_{13}O_5N$, which contains COH_2 less than the former. Proescher suggests that it may be a formyl glucosamine, or the acetyl derivative of the hitherto unknown pentosamine. Pappenheim[2] suggests that it may be urobilin, but I propose to return to this point presently. Proescher found that it was practically useless to attempt to isolate this body directly from the urine. As I shall mention later, Ehrlich now thinks that the chemical reaction takes place by the union of dimethyl and a part of a pyrrol ring. The reaction takes place roughly as follows:

$$C_6H_4\begin{cases}N(CH_3)_2\\COH\end{cases} + H_2X = C_6H_4\begin{cases}N(CH_3)_2\\CH=X.\end{cases} + H_2O.$$

The dimethyl attaches or anchors the unknown body, according

[1] 'Zeitschrift für physiolog. Chemie,' Bd. xxxi.

[2] 'Berl. klin. Woch.,' January 12th, 1903.

to Ehrlich, by means of a methylene group and not by an amido group, since other methylene compounds, such as phloroglucin, phenyl, methyl, pyrazolon, join with dimethyl and form red-violet compounds. The addition of formaldehyde to the urine prevents the reaction, the formaldehyde occupying that group to which the dimethyl compound attaches itself. The same occurs if one adds pyrogallic acid (trihydroxyl benzene), in which case the benzene group is probably disturbed. Salicylic acid, oxybenzoic acid, and gallic acid do not behave in this way. I tried to ascertain if the trihydroxyl combination altered the unknown body. To some urine containing a fair quantity of the unknown body I first added pyrogallic acid, and then a few drops of an acid solution of dimethyl, and to this some ferric chloride. The pyrogallic acid combined with the ferric salt, forming a claret-coloured body; I then shook up the mixture with chloroform. Had any of the red combination been present this would have been partly claimed by the chloroform, as it sank to the bottom, but the chloroform remained uncoloured; this appears to indicate some splitting up of the unknown body. Proescher describes three characteristic spectrum bands in his publication which the solution of the red combination body gives between D and E, to the blue side of B, and to the red side of F.[1] After exposure the first and third bands faded and disappeared, while the central one increased in distinctness. The red substance is amorphous, is soluble in alcohol, chloroform, acetic acid, epi- and di-chlorhydrin, is little soluble in water, and is insoluble in benzol, toluol, ligroin, and ether. In alcoholic picric acid solution it falls as an amorphous brownish-red precipitate. In ammonia and caustic potash it is soluble, and gives a yellow solution, which can be turned again into the red colour by the addition of acids. Heated in concentrated hydrochloric acid or diluted sulphuric acid, it decomposes slowly. Ehrlich and Proescher suggest that the reaction should be carried out by adding a few drops of a 2 per cent. solution in hydrochloric acid and water (dimethyl 2, dissolved in HCl 50 c.c., and add water to 100 c.c.) to the urine in the cold, the red colour appearing in a few minutes. Since heating only slowly decomposes the red body, I have found it more useful to apply the test slightly differently. To 1 c.c. of urine, heated to

[1] At λ 559, at λ 510, and at λ 492.

frothing, I drop, by means of a measured pipette, drops measuring ·01 c.c. slowly one after another, just giving sufficient time between the drops to allow all the colour to appear, which takes place rapidly when the urine is hot. In this way the first trace of colour can be noted, and after a certain number of drops have been added the change of colour from cherry-red to brownish red or brown can also be fixed. As I shall presently show, the clinical use of the reaction depends upon the possibility of determining the degree. I distinguish the degrees of reaction as follows:—A positive reaction is present when 1 per cent. of the reagent produces a red colour, when the first drop is seen to fall through the urine like a red worm, or when the froth is tinged pink on the addition of more drops; the colour increases in intensity in positive reaction up to 5 per cent., and at times even up to 25 per cent.; at times the colour first appears on the addition of 2 per cent., and reaches its maximum between 5 and 8 per cent. However interesting this may be, it must not be confounded with a positive reaction, and I therefore call this a colour-change of the second degree, and when the colour only appears with 3 per cent. a colour-change of the third degree. All other changes of colour may be discarded as of no clinical importance. Clemens[1] tested a number of urines, using only the cold method, and as far as one can judge merely depended on the intensity of colour when a "few drops" of the reagent were added, and on the intensity of colour of the chloroform solution. His results are somewhat different from mine, and I attribute this to the want of method capable of distinguishing between the degrees of coloration. He obtained a reaction in 19 per cent. of all his pathological cases. This is higher than the percentage which I obtained while I was not selecting cases for the reaction, but lately I have not applied the test to those conditions which never gave a reaction in my first 250 cases, and therefore a general percentage is of no importance. He believes that in no disease is the reaction constant, nor was it constant (as a rule) in any one patient. I believe that I am able to explain the reason of this. He finds it largely in gastro-enteric affections, especially in inflammatory conditions. In 75 per cent. of summer diarrhœa he obtained good reactions, while pure gastritis and pure enteritis gave no

[1] 'Arch. f. klin. Med.,' 1902.

reaction. Six cases out of nine of appendicitis gave occasional reactions. In a similar manner, in pneumonia, pleurisy, empyema, tuberculosis, some gave reaction and some did not. Engel, of Davos, says that the reaction is positive in acute gastro-enteric disturbances, and that it is frequently positive when the diazo reaction is positive. Tuberculosis in itself does not necessarily cause a positive reaction, and frequently in phthisical patients the reaction is positive on admission, and disappears in a few days. He finds the specific gravity high when the reaction is positive, but fails to intensify the reaction by increasing the specific gravity by evaporation. I have obtained good reactions in urines with a specific gravity as low as 1006. Koziczkowsky[1] has also examined a large number of urines, and carries out the test as follows:—He fills two test-tubes one third full with urine and adds formaldehyde to one; into both of them he drops eight to ten drops of the reagent, and distinguishes five degrees of coloration, viz. brandy-and-water colour, brandy colour, pink, light red, and dark red. He regards the pink as the transitional stage, and the light and dark red as pathological. His clinical results in the main appear to agree with mine.

Dealing with gastro-enteric conditions, I applied the test in 43 cases of typhoid fever, 8 of which were still in the pyrexia stage, in 3 cases of appendicitis, in 1 of lead colic, in 1 of simple peritonitis, and in 5 of gastritis, as well as in a number of functional gastric disturbances. Of the 8 typhoid fever patients in the acute stage, 7 gave some colour reaction, 2 of these gave very distinct positive reaction in the cold (at this time I was not using heated urine), and 5 gave less good reaction. I see from my notes that the 2 positive reaction cases were very acutely ill, both in relapses, and the prognosis was considered serious. Of the 3 cases of appendicitis all had abscess formation; in 2 the pus was draining and their urines gave no reaction, while the third was complicated by a fæcal fistula and pneumonia; here I got a positive reaction. Of the gastritis cases, 3 gave colour-changes of the second and third degree, but none gave positive reaction. The urine of a few children suffering from a febrile disturbance due to faulty assimilation or doubtful milk gave no reaction, nor did any of the other cases mentioned. Unfortunately I was unable to obtain any urine of patients suffering from

[1] 'Berl. klin. Woch.,' November 3rd, 1902.

summer diarrhœa. One diabetic gave a colour reaction of a second degree, and one gave no reaction. Among the cases of disease of the urinary apparatus not a single one gave any reaction. In marasmus no reaction was obtained, and of all the cases of disease of the nervous system, 1 case of neuritis and 1 case of probable hysteria gave colour-changes of the second and the third degree respectively. The urine of the former of these cases presented a peculiar pigment. Likewise no reaction was obtained in surgical conditions, sarcoma, carcinoma, anæmia, osteo-arthritis, psoriasis, and the like.

In acute infective processes—rheumatic fever, rheumatic endocarditis (of which more will be said later on), morbilli (2 cases only), variola, erythema nodosum—the urine gave no reaction. In 4 cases of pneumonia, 2 gave a colour-change of the third degree, and 2 gave a positive reaction. One of the latter was a boy of fifteen, who was extremely ill on the eleventh day, and in the second case the diagnosis read tubercular pleuro-pneumonia. Five cases just convalescent of pneumonia gave no reaction. In 3 cases of diphtheria during the acute stage, 1 gave a colour-change of the second degree; this case was a moderately bad one. The other 2 had been treated apparently with success by antitoxin. Thirteen cases of diphtheria in the post-pyrexial stage gave no reaction. Of 6 cases of acute scarlatina, 1 gave a colour reaction of the third degree, 2 of the second degree, and 3 no reaction. None of the convalescent scarlatina cases gave reaction. One case of vaccinia with marked pyrexia gave a positive reaction, while all other cases gave no reaction. It must, however, be stated that this patient was admitted into hospital with the diagnosis of typhoid fever, and at the time of testing was acutely ill. One case of subacute rheumatism gave a colour-change of the third degree. I examined the urines of 85 patients suffering from pulmonary tuberculosis; of these 25 gave some distinct colour-change, while 16 gave change up to the third degree. One case of acute phthisis, in whose sputum, I was informed, were found many cocci, gave a strong positive reaction, while in a second case of the same condition, in which tubercle bacilli were found practically in pure culture, no reaction was obtained. In all, 8 gave positive reactions. These were all cases with marked toxæmic aspect, and, if one can draw conclusions from physical

examination, almost certainly cases of mixed infection. One patient, however, was said to be improving; whether she continued or not I cannot say. In one case of tubercular adenitis and old hepatic cirrhosis a positive reaction or possibly colour-change of second degree was obtained. In miliary tuberculosis I got no reaction. Among the cases of bronchitis, bronchiectasis, one gave me good change of colour in the cold; I cannot say whether this case should be classified under positive reaction or colour-change of second degree. No reaction was obtained in cases of acute bronchitis, laryngitis, and emphysema. At first it appeared as if influenza increased the unknown body in the urine readily, but this soon proved to be due to the antipyrin which I prescribed freely for the pains. In all cases I obtained a colour-change of the second degree save one, in which there was a positive reaction. This case was complicated by gastric symptoms and delirium.

In chronic valvular heart disease, as I expected, no reactiou occurred, but in one case of aortic aneurysm I obtained a "slight colour-change" in the cold, which in all probability does not amount to the third degree. In rheumatic endocarditis I have tested repeatedly, but always failed to find the reaction; but in infective endocarditis I have obtained a good reaction in each of the three cases. One of these certainly is peculiar. When first I had the opportunity of testing his urine the pyrexia was remittent, the patient extremely ill, and the clinical prognosis as bad as it could be. Shortly after this the patient was treated with antistreptococcic serum, and in the course of a week or two improved greatly. I was fortunate enough to be able to test his urine when the temperature was again normal, and no reaction could then be obtained.

During a normal pregnancy I have never been able to find a reaction. In normal parturition, too, the urine is unchanged; but in sapræmia and septicæmia things are different. In early septicæmia the reaction is positive; in some later cases I failed to obtain it; I propose to return to this presently. In sapræmia I obtained a reaction in 1 case, colour of the third degree in 1 case, and no reaction in 2 cases. The clinical prognosis in these cases was good, without treatment, save in the first case, in which treatment by intra-uterine douching was thought

necessary. In this case I obtained a very slight colour-change in the milk.

With regard to the diazo test, I may mention here that I have tested several of the urines side by side, and find that only rarely do the diazo and dimethyl-amidobenzaldehyde tests coincide. I have tested over 350 urines, and in looking over my results I find that a positive reaction occurs when the temperature is raised, when the patient is acutely ill, and generally while sweating is going on. This latter fact led me to consider whether sweating in itself could produce an increased quantity of the unknown body in the urine; and I therefore performed two simple experiments on myself. In the first I injected some pilocarpine nitrate, and succeeded in perspiring freely. Urine was passed immediately before the injection, two hours later, and eleven hours later. Although no distinct reaction was obtained in any specimen, the urine secreted during the sweating period was distinctly more coloured than the other two. The second experiment was made with urine secreted during violent exercise (mowing long grass). The control urine was passed some hours later. The result was approximately the same as in the first experiment. It therefore appears that tissue-destruction is capable of either manufacturing this body in larger quantities or of sending larger quantities through the kidneys. My later observations have led me to believe that certain forms of tissue-destruction are necessary to produce sufficient of the body to constitute a reaction. This form of tissue-destruction is mostly due to a profound toxæmia, and I believe is more often due to a coccic toxæmia than to any other kind. Mixed tubercular infections, sapræmia, septicæmia, abscess around the appendix, infective endocarditis, give good positive reactions. Colour-change of the second degree, too, usually indicates the same destructive changes, sometimes in response to the action of coccic toxins, as in scarlatina, and sometimes in response to other noxious agents. Clemens, too, regards the reaction as due to increased metabolism, but Koziczkowsky, having experimented with rabbits during periods of fasting, in which he ascertained that there was heightened destruction of albumen, and failed to obtain a reaction, states that if increased disintegration of albumen produces the unknown body, it must be very great.

I have already stated that Clemens believes that in no disease is the reaction constant. According to my views the body which gives rise to the reaction is a product of destructive metabolism of a specific kind, and would be capable of being further split up by an excessive action of the poison. I attribute the fact that in a fatal case of septicæmia (puerperal) I did not get a trace of colour-change to this continuous splitting up. I have not met with a case of infective endocarditis which has failed to give a reaction, but can easily conceive that this could take place in some moribund cases.[1] The inference, therefore, which I draw from this is that a positive reaction indicates a grave prognosis, not necessarily a hopeless one, for active treatment may be capable of removing the source of the toxin, and the organism may repair the damage already done, but always one which should put the physician on his guard. Colour-change of the second degree may assist one to a correct diagnosis if the other factors of the case are carefully considered. I will go further in the case of positive reaction when there is clinical evidence of endocarditis, and say that even if no cocci can be found in the blood, the case is infective and not rheumatic.

I have suggested that the unknown body in the urine is a product of destructive metabolism, and in order to support this view I attempted to trace it to the tissues. The fact that small quantities were found in the milk, saliva, and sputum of patients does not prove that it is not formed in the kidneys, since "internal secretion" might answer for this appearance. Clemens states that the reagent when taken by mouth does not colour the urine. I examined rabbits which had been injected with emulsions or fed with the raw chemical. Before doing so I was able to determine that the unknown body was present in the urine of rabbits. A rabbit was injected with streptococci and died on the following day; the urine taken after death gave slight change of colour, but no clinical reaction. More colour-change was found in the urine of a rabbit which had died of tubercular infection, but even here it did not amount to a colour-change of the third degree. A rabbit was fed with 0·5 dimethyl-amidobenzaldehyde and killed four days later; I had

[1] In one case of infective endocarditis in the *post-mortem* room I obtained a few drops of urine which apparently failed to give a reaction. The cartilage in this case stained fairly well.

hoped that the hydrochloric acid of the stomach would have dissolved the reagent, and the solution would have been carried off by the gastric lymphatics. In spite of a careful search I failed to detect any tingeing of any of the tissues. A rabbit was then injected with an emulsion containing about one gramme of dimethyl-amidobenzaldehyde, in two doses subcutaneously. The first dose was slowly absorbed, and apparently produced but little change in the rabbit; but the second produced a very marked reaction, and the rabbit became peevish. Before it was killed one noticed a peculiar bluish staining of the hair around the site of injection, and a fair number of bald patches. The tissues were treated with hydrochloric acid after dissection, but although I obtained a minimal reddening of the urine no trace of coloration of the tissues could be found. I next dealt with a rabbit which had died five days *post injectionem* of diphtheria toxæmia. The various tissues were kept for several days in alcohol, and coarse sections were then cut and treated with acid solutions of the reagent. Brilliant violet-red coloration appeared in the cartilage; under the microscope this appeared as a diffuse coloration of the perichondrium and the matrix. The cells and the dense fibrous tissues remained uncoloured. White matter of the brain and spinal cord was tinged a pretty mauve, the membranes and the cells remaining uncoloured. The mesentery and mesenteric glands appeared of a pale mauve colour, while after a considerable time both kidney and liver took on a pale pinkish tint. The capsule of the kidney became a very pale mauve colour as did muscle, but spleen, bone, vitreous, and skin remained uncoloured. The urine of this rabbit gave a fair reaction *post mortem*. Ehrlich first pointed out that the unknown body may be found in cartilage, and especially perichondrium. I found that it is present in smaller quantities in other tissues, such as white matter, kidney, liver, and mesentery. The urine contains it in solution. Now under normal conditions but little can be found in the urine, and in the tissues of a rabbit one can only obtain marked colour-change in the perichondrium. I found very brilliant coloration in the cartilage of a pig which had been fed on the sputum of human tuberculosis. The cartilage of a dog, dead of distemper, gave a less bright colour. If it were formed in the perichondrium it would be difficult to explain how it appears

nearly constantly in normal urine, and also how it is increased by such divers causes as various toxins, etc. It appears much more feasible to suggest that the destruction of the protoplasm of all the body cells in the process of metabolism yields a large number of products, one of which is this unknown body. Its increased production will follow on certain causes which act destructively on the tissue-cells. The kidneys are capable of passing a certain quantity of this substance through them in the urine while the surplus is stored up in suitable places. Perhaps the substance loosely joins certain fluids, such as mucoid, cerebro-spinal fluid *inter alia*, and then it would be found wherever an appreciable collection of the fluid is present. I feel inclined to believe that this takes place, as it would fully explain the intense coloration in perichondrium, and the lesser tinctorial changes in the other tissues.

Returning to the chemistry of the reaction, it appears to me to be unlikely that the unknown body should have the character of a glucoside, especially as I failed to get any reaction with any other glucoside in the test-tube, nor did any diabetic urine give it. The empirical formula of the unknown body given by Proescher of $C_7H_{15}O_6N$ is probably too simple. Dimethyl(p)-amidobenzaldehyde gives a similar but weaker colour reaction.

Papenheim[1] suggests that the unknown body is either urobilin or a substance which constantly accompanies it. He bases this suggestion on his observations that in those urines which give Jaffé's and Gerhardt's tests the dimethyl reaction is also present, albeit at times more intense; that ordinary uro-erythrin does not produce the reaction, and yet urines which give the reaction are nearly always highly pigmented. Koziczkowsky, too, noticed that many pigmented urines gave positive dimethyl reaction and tested for indican quantitatively, but with no convincing results. The view that urobilin may cause the reaction is further strengthened by Ehrlich's belief that the chemical combination takes place by means of a pyrrol ring. The chemical constitution of urobilin is $C_{32}H_{49}O_7N_4$,[2] and it is quite possible that among other substances it may produce a red colour-body. Ehrlich says that the colour-change is increased after

[1] 'Berl. klin. Woch.,' January 12th, 1903.

[2] According to Dr. Garrod this formula (*i. e.* that of hydrobilirubin) is too simple.

excessive smoking, in response to a union with nicotine, another pyrrol derivative (pyridin). Papenheim failed to obtain a change of colour in the filtrate of urines after precipitation with lead acetate. This he thinks strengthens his urobilin theory. Since choletelin is not precipitated by lead acetate, he comes to the conclusion that this substance is not the body we are seeking. I obtained some specimens of horse's urine, which, as Papenheim points out, is supposed to be free from urobilin. The urine of a horse suffering from tetanus gave me a good reaction. After precipitation with acetate of lead the filtrate was acidified, and gave me a very clear reaction. Jaffé's and Gerhardt's tests were both negative. In a non-pathological urine, which gave some change of colour, the filtrate, after precipitation by lead acetate, also gave a change of colour. Urobilin is always increased in the urine of pyrexia, but the dimethyl-amidobenzaldehyde reaction does not show this constancy. I therefore believe that one can reject the urobilin theory. Indol gives a reaction with dimethyl-amidobenzaldehyde in the test-tube according to Clemens, but since this substance is not found in normal urine this cannot be the body which we are seeking.

Although compounds containing a pyrrol ring do join with the dimethyl(p)-amidobenzaldehyde in the test-tube to form red colour-bodies, compounds containing benzol rings also do so, *e. g.* salicylic acid, phenol, etc. I have been able to distinguish between the colour of antipyrene-dimethyl, phenol-dimethyl, and the unknown body-dimethyl, compounds.

As you may have noticed, I have persistently called the substance which joins with the dimethyl(p)-amidobenzaldehyde to form the red colour-body in urine the "unknown body." This I have done because I believe that we are dealing with a substance hitherto unknown. While there is evidence that several substances may form red compounds with the salt, I am of opinion that only one body gives the reaction which I have described as pathological. *March 3rd,* 1903.

24. *The clinical and pathological characters of veld sores prevalent amongst the troops in South Africa.*[1]

By N. Bishop Harman.

Clinical Investigation.

Description of the sore.

The veld sore, in the state in which it is most commonly seen, is recognised as an extremely superficial ulcer, edged by a fringe of exfoliated epithelial tissue and an areola of inflammatory redness. To this sore is attached a history of—for such an ulcer—great age, yet there is often little or no evidence in support of such a statement. It is not often that the surgeon sees the sore in its initial stages, and when for the first time he gains sight of the earliest stages, there is a genuine feeling of surprise.

Mode of onset.—A man has been for some weeks on the veld, the free open life and constant exercise, and the relish of hunger for the rations of biscuit, beef, jam, and tea, together combine to make him feel as "hard as nails"—"never so fit in his life." Notwithstanding this feeling of fitness, he notes that the trivial scratches and abrasions on the backs of the hands, incidental to the rough work of the march and camp, do not heal in the easy manner they had done hitherto. Instead, he finds that the site of a trifling scratch, got in opening a biscuit tin, in adjusting his saddlery, or what not, becomes inflamed, there is a pricking or burning sensation, and alongside the scratch-mark there appears a delicate blister, the blister bursts, and a veld sore remains. Even the slightest abrasion will become so changed, until his hands and legs may present a mass of sores.

The blister and its contents.—Following the clinical history of one such blister, it is found to be formed by a covering of epidermis, which is usually so thin that the character of the subjacent fluid can be judged. Around the blister and the scab

[1] Coloured figures illustrating this communication, with more minute details of the cases, will be found in the 'Journal of Pathology,' 1903.

marking the site of the abrasion is a ring of redness, indicating inflammation; the ring is usually narrow, the colour rapidly shading off into the bronzing of the skin. The blister steadily increases in size, so that in bad cases, in so short a time as forty-eight hours, it may be larger in circumference than a shilling piece. It will be shallow and flaccid, or raised and tense, according to the quantity of its fluid contents.

The blisters, however, more commonly grow slowly and burst at a stage earlier than this, when about the size of a threepenny or sixpenny piece; either by the pressure of the contents, the rub of a "protecting" bandage, or an accidental knock, and there issues from the blister a serous or sero-purulent fluid, either quite thin and watery or slighly viscid; the consistency of the fluid contents depends upon the duration and rate of growth of the blister; if of slow growth or long duration it is inclined to viscosity, if of rapid growth it will be found thin and watery.

The chronic sore.—The ulcer resulting looks very like the floor of a freshly opened cantharides blister, save that in the veld sore the ragged edges of the epidermis appear rather more sodden, and under the recess formed by the epithelial edges the presence of flecks of pus within the serous discharge may be detected. Here the resemblance ends; the ulcer arising from the cantharides blister will heal in a few days, whilst that of the veld sore will drag on a miserable existence for months, steadily spreading the meanwhile, until it may cover nearly the whole of the back of the hand, and this notwithstanding much professional and amateur treatment. When it has dragged on for some time, and suffered many things of many hands, the floor of the ulcer loses its fresh clean appearance, and assumes a tough, non-vascular character, not unlike that of old parchment; the edges retain a fresher appearance, and scraps of overhanging epidermis may still be noted.

It is during this time that the veld sore not infrequently commences to exude pus fairly freely, probably by reason of a secondary infection; then a common ulcer involving the true skin may result, though even under this condition the edges of the ulcer retain the typical superficial character of the veld sore.

I do not mean to suggest that throughout these months no

sign of healing has appeared; far from it, many a time the ulcer will have rapidly scabbed over after the application of some nice clean dressing, but after a few days the apparently healthy scab will be found to rest upon a bath of thin, slightly purulent fluid, and thus the ulcer may be laid open again and again. It is perhaps these frequent disappointments which induce the men to take the matter in hand themselves, for there has grown up around the sore a whole pharmacopœia of "infallible" specifics—such as sugar and soap, train oil, olive oil, vaseline, paraffin, tar, "wait till it dries up," "don't wash," etc. etc. Some of these "specifics" are not, indeed, so far-fetched, *e. g.* the tar, though the results of its application are the reverse of infallible, as might be expected from the failure of purified and valuable antiseptics; even the "don't wash" advice may perhaps be excused when water is so liable to contamination.

Symptoms other than local.—It was rarely that the sore produced any other than local manifestations; in by far the greatest number of cases there were no indications of septic absorption, yet I have seen cases where the absorption of septic material produced both lymphangitis and lymphadenitis; but in all these cases the sores had commenced to exude pus freely, perhaps as the result of a secondary infection.

In one case, seen in Pretoria, of numerous dirty sores on the legs, there followed intense redness and pain along the course of the lymphatics towards the triangle of Scarpa, with tenderness of the glands at the apex of the triangle; but the vigorous cleansing of the sores and local applications over the lymph paths resulted in a subsidence of the inflammatory symptoms. In another case of multiple and dirty sores (there were twenty-nine over the two shin and peroneal regions), the gland at the apex of the triangle of Scarpa became inflamed, suppuration ensued, and a bubo formed which had to be incised and the pus evacuated. In both these cases the soldiers (volunteers) were young, immature, and worn out.

I could not find that there were any general or constitutional symptoms attending the existence of the sores; without doubt general weakness and malaise were associated with their presence, but these symptoms were more reasonably referable to the condition of life, food, and work of the men, than to the effect of the sores; indeed, there is strong evidence to show that

the appearance of the sores is an indication of the existence of a loss of general tone or condition. Certainly in my own case, where by inoculation from a very severe case of veld sore I produced the sore on my arm, there were no constitutional symptoms.

Minute herpetiform blisters.—Here I must note another means whereby veld sores are produced, one which has so impressed itself upon the mind of my sometime fellow-student, Mr. Harland (3), that he would prefer to reserve the name "veld sore" to those sores alone which arise in this manner. In my experience, however, this has been a rare mode of origin in comparison with the onset subsequent to an accidental abrasion.

I refer to minute herpetiform blisters occurring only on the hands. The covering of these vesicles is very thin, so that in their exposed position it is speedily broken, and very frequently veld sores follow on at the site of the broken vesicles.

I was at some pains to ascertain the cause of these minute blisters, and it appears they arise in three ways: (1) immediately subsequent to insect bites; (2) on hands which from much sunburn have become tender; (3) in the immediate neighbourhood of old or open veld sores.

As regards the first of these classes, I saw cases in which the initial minute blister followed the bites of the common brown horse-fly; in other and more frequent cases the bite of a mosquito was the irritant; in one such case, that of a major of Yeomanry, the mosquito was observed in the act of biting, the site noted, and in this place the minute blister found, which later broke and became secondarily a veld sore. In all these cases there was no precedent or coincident veld sore of the ordinary type.

In the second class—the effects of sun—here, without precedent or coincident veld sores, one or two minute blisters appeared on the hands, which were inflamed and very tender from exposure to sun and wind; these, after rupturing, were in some cases followed by the ordinary veld sore.

Lastly, the minute blisters occur in the neighbourhood of the ordinary veld sore produced in the common manner by abrasion. These little blisters were especially liable, indeed, almost certain to become veld sores upon rupturing.

In each of these three classes the causation of the minute blisters is really the same—irritation, the insect bite, the burn of sun and wind, or the general irritability of the skin in the neighbourhood of the veld sore; consequently there is every reason to expect one of the signs of irritation of the epidermis, namely, vesication or an herpetiform eruption, whilst the solution of continuity consequent on the rupture of these minute blisters affords ready ingress to the presumptive organism of the veld sore.

I made a special note of a couple of these cases. In one of them I was able to protect aseptically two such minute blisters in an undamaged state for several days, and during this time and under these circumstances they showed little or no tendency to change their character, whereas in the blister arising adjacent to abrasions the growth is often exceedingly rapid.

In the bacteriological examination of the two cases, in one in which there were numerous coincident veld sores film preparation showed the presence of a very few dots in pairs which may be cocci, similar to those found in the ordinary veld sores; the second case, showing scars of old but healed sores, and which was aseptically protected, showed a very few dots singly, and one or two pairs which may be cocci. I had no opportunity of making a bacteriological examination of these minute blisters in cases where there were no precedent or coincident veld sores. I am inclined to believe that these minute blisters act in the main by affording an abrasion on rupture. I do not mean to assert that a veld sore may not arise directly in this form; indeed, one would reasonably expect that the dirty horse- and blow-flies would convey infection by their bites; but in the numerous cases of the sores which I examined there was no difficulty in ascertaining the history of, or in seeing the site of an abrasion, whilst there was an equal certainty of the occurrence of veld sores where neither flies, ticks, nor minute blisters were to be seen.

Sites of the sore.

The most frequent site of the sore is the extensor surface of the upper extremity from elbow to digits; the corresponding region of the lower extremity is affected to a very much less degree.

Seat of election.—By far the greater number of sores occur upon the backs of the hands and wrists; in cases where they are present in these regions they may be found extending up the forearm, and in a few cases the forearm alone is affected. In a few cases I have seen the sore as high as the elbow, and in one case only over the inner border of the biceps tendon, above the inner condyle of the humerus. They are found upon the lower extremity from the ankles up to the knee; here the extensor surface is again the usual site, particularly towards the peroneal surface.

The reason for the seat of election—the dorsum of the hands—is not far to seek; it is the place above all others most liable to knocks, scratches, abrasions, and slight wounds.

The "general condition" favourable to the growth of the sore.

The climate of the high table-lands of South Africa which constitute the greater portion of the territory of the new colonies, and which is commonly known as the high veld, is by reason of its dryness, and the comparative scarcity of vegetation and animal life, a region not favourable to the multiplication of micro-organisms—a factor which has long been recognised in connection with tuberculosis, and which many of us believe to be accountable in some degree for the comparatively few cases of sepsis in gunshot wounds received in these regions. Yet it is here almost exclusively the veld sore appears. Further, it rarely appears save under some such conditions as those of war, when individuals, being cut off from their normal base of supply for long periods, are obliged to subsist upon such preserved foods as they can carry with them. The disease was unknown to the Boer farmer dwelling on his farm on the high veld, but it was known to the explorer who, trekking miles from civilisation, lived upon such food as he could carry; it was known to Briton and Boer when on the war-path against Matabeles, and rarely it has appeared in town districts when by peculiar conditions the supply of natural fresh foodstuffs has been cut off.

Occurrence apart from war.—That the sore was known before the war I have on the testimony of several gentlemen. Mr. W. Robertson, lent by the Colonial Government for Imperial service during the rinderpest in 1897, states that he and his party

suffered severely from the sores when amongst the Kaapberg Mountains, Bechuanaland. The scars of the sores remain on his wrists to this day. He further noted that they arose from abrasions, and that there were no ticks in the place; also the long duration of the sores, and their resistance to treatment when on the trek. Mr. R—, prospecting in Gwalo, Matabeleland, in 1896, suffered from the sores, which he states would not respond to any treatment whilst on the trek, but which healed readily and without treatment on returning to Kimberley and good food. Dr. Darley Hartley, who has been in South Africa twenty years, tells me that in East London, during the rinderpest of 1894, all communication by means of ox waggons was forbidden, so that from lack of transport the supply of vegetables and fresh milk was practically stopped. Coincident with this was a large outbreak of sores amongst the working population; of these sores 90 per cent. were veld sores, the remainder were the more or less endemic "Natal sores" and boils.

A scorbutic condition.—The general condition, I think, may be fairly described as a scorbutic one. The food of the modern army has been improved to such an extent that scurvy proper is a thing of the past, but there remains a sufficient unnaturalness about the improved dietary to cause reduction of the resistance of the men to the attacks of certain infective organisms.

On the immunity of coloured men.—That the immunity of the Indian and black races may be explained on similar grounds is, I think, possible.

The scrupulous care with which the Indian adheres to his meagre dietary is notorious, and he is by no means bashful in soliciting attention to his wants in this direction.

I was for long at a loss for any definite reason to account for the almost complete immunity of the blacks; the explanation may be found in the following statement:—Mr. R—, artist, travelling in Matabeleland in 1896, suffered from veld sores himself, but none of his black servants were affected; he noticed that they ate flowers and green stuff of any sort, and that they would pluck and eat even as they marched.

Immunity not conferred by one attack.

Apparently an attack of one or more sores occurring within a short space of time does not confer any degree of immunity against subsequent attacks.

If a man contracted one veld sore, it was almost certain he would get a succession of others by auto-inoculation within a comparatively short space of time. I have frequently counted as many as thirty sores in various stages on one man. Trooper T— had twenty-nine on the legs only.

I have seen very many cases where the hands presented scars, old sores, recently formed ulcers, and quite fresh and unbroken blisters.

Further, I find that a man may suffer from a second crop of the sores within six months of the first outbreak. I found examples of this in both privates and officers.

That the passage of a longer period of time has no effect is shown from such cases as that of a patient who had attacks in 1897 and in 1900, and by several such histories I had from Boer veterans.

THE MODE OF HEALING.

The scar.—The tissue alterations are extraordinarily slight for so long-continued a lesion. The skin is noticed to have lost some of its usual healthy "nap," which is replaced by a slightly satin-like feel; it is thinner; it is rather less elastic, for it wrinkles on being slightly displaced; the hair has regrown, but it is not so plentiful as it should be; there is a purplish pigmentation, proportionate to the duration of the sore, and always greater in the scars of sores on the lower extremities than on the upper.

These facts, the almost simultaneous growth of epidermis beneath the dry, silver-scaled scab from centre to periphery, and the regrowth of the hair, show that the whole epidermis is not involved in the sore, *i. e.* the sore arises within the layers of the epidermis.

Further, that there is some change in the true skin following on the epidermal irritation is shown by the slight thickening of the skin in the earlier stages, and the thinning of the skin and loss of elasticity in the later stages of scarring.

The Pathology of the Lesion.

Experimental inoculation in man.

1. *From the blister fluid.*—On the fifth day after the collection of the fluid from the blister of Case 5, shown on cultivation to be a pure culture of cocci, I inoculated myself with some of the original fluid.

An area of skin on the extensor surface of the left forearm was shaved, sterilised by washing with 1 to 1000 solution of mercuric chloride, then vigorously washed with sterilised water.

The epithelium was then scraped away with a sharp sterilised knife from an area 1 × 10 mm., until there was a slight oozing of blood-stained serum. Two loopfuls of the blister fluid were lightly rubbed into the abrasion with the platinum loop, and left to dry. The arm was wrapped in sterile wool and bandaged; it was so protected during the whole course of the experiment.

Five hours.—The site of inoculation shows a red areola; there is slight itching and smarting.

Sixteen hours.—A small bleb like a seed pearl has appeared at one end of the abrasion.

Twenty-nine hours.—The bleb has extended so as to close one end of the abrasion; the abrasion has scabbed.

Forty hours.—The bleb has increased in size. There is no pain.

Sixty-six hours.—The bleb has ruptured. From the fluid contents, which appear to the naked eye as plain serous fluid, film preparations and a culture were made. The film shows a fair number of pus cells, and some epithelium *débris;* there are a few cocci disposed as diplococci, which have an appearance of capsulation. The culture grew in twenty-four hours, showing several discrete colonies which turned yellow, and proved to be composed of cocci, disposed as staphylococci.

Four days.—The free edge of the ruptured bleb appears to be gummed down by dried discharge; the raw surface is scabbing.

Five days.—No change; seems likely to heal without further progress.

Seven days.—Spreading fairly rapidly; no subjective symptoms.

Eight days.—Quite a large blister of horseshoe form surrounding the scab; it is about the size of a sixpenny piece. The bleb was opened aseptically, films made, and agar smears placed for incubation.

Films.—Show few pus cells, but numerous epithelial cells; the cocci are numerous, and disposed as diplococci, with a suggestion of capsulation; a few tetrads are seen, also diplococci in clusters and short chains.

Culture.—In twenty-four hours showed a vigorous growth as a rich paint-like streak; it consisted of a pure culture of cocci.

Nine days.—The sore itched very much, so as to be an annoyance. I therefore stripped off the whole of the epidermis of the blister and its surroundings as far as possible, also removed the scab, leaving a clean-looking raw surface, which oozed blood at a few points. This was covered by aseptic lint and strapped.

Eleven days.—The site of the sore is covered with thin silvery scales of dried epithelium and serum.

Thirteen days.—The silvery scales covering the site were rubbed off; beneath was found a shining bluish-pink healed surface. The area is slightly thickened to the feel on pinching it up.

Two months.—The scar is plainly visible as a bluish-pink stain; the hair has regrown.

Four months.—The scar is still plainly visible.

Throughout the whole duration of the sore there were no constitutional symptoms or suggestion of lymphatic infection.

2. *Inoculation from remote generations of subcultures of the coccus grown from the lesion.*—On my return to England the various cultures brought home were examined, and replated as a precautionary measure. All were alive after two months' sealing in tubes of agar, gelatine, and broth. All were pure except one, which had been opened *en voyage* home.

Experiment I.—The skin of the arm was sterilised, an abrasion made, and some of a tenth subculture rubbed in. Only a slight inflammatory reaction resulted, which lasted two days. On the third day the scab was torn off, and films and agar smears made from the lymph exuding from the wound. The films contained

diplococci, and the cultures showed numerous yellow colonies, identical with those previously described.

EXPERIMENT II.—A further attempt was made with a subculture which had been grown on agar smeared with my own blood; from this there resulted the same inflammatory reaction, and two minute vesicles at the edge of the abrasion; these dried up on the third day.

EXPERIMENT III.—Another attempt with a tenth subculture of another line of descent was made on my arm, and on that of another gentleman; on my arm there was an increase of the inflammatory reaction, but beyond this nothing resulted. On the third day the scab was removed, and films and cultures made from the lymph exuding from the wound, with results identical with those found in Experiment I.

EXPERIMENT IV.—Attempts were then made to increase the virulence of the culture. Three generations were grown in broth and on agar alternately, to which had been added two or three drops of my own blood; the cultures gained distinctly in luxuriance. From this third blood subculture (fourteenth from start) a fresh inoculation was made on the dorsum of my wrist. A control culture was made from the inoculation culture, which in twenty-four hours showed a rich growth of pure cocci.

First day.—Considerable burning and smarting subsequent to the inoculation. At the end of the twenty-four hours there was no change other than a considerable inflammatory reaction. A portion of the control culture was placed on the wound, and pricked in with a surgical needle.

Second day.—During the next ten hours the irritation was marked; on examination at the end of this time there were found at one end of the abrasion three vesicles spreading out from the edge; in appearance they were identical with the vesicle at the early stage of the inoculation from the blister fluid (p. 204). At the end of the twenty-four hours one vesicle was opened and examined. The film shows a fair number of cocci in pairs, and much epithelial *débris*. Cultures on agar and in broth had both grown well in twenty-four hours, the former being particularly luxuriant, of a light brownish-yellow tint, and very like the original rich growth from Case 5, from which the inoculation culture was derived. The growths were composed of cocci.

Third day.—The two vesicles remaining have united, and spread eccentrically; their appearance is similar to that shown in Fig. 15 *c*. Towards the evening of this day the combined vesicle had spread slightly. The following morning it was found flattened and shrunken, probably from being overlaid. The vesicle was opened, and films and cultures prepared. On the evening of the fourth day the scab over the abrasion and the loose epidermis of the vesicles were torn off; it was found that the epidermis for a considerable area around the vesicles was very easily stripped off, showing that a softening of the epidermis had been produced beyond the extent of the vesication; this stripping could not be performed to a proportionate extent around those parts of the abrasion where vesicles had not appeared. The ease with which the epidermis was stripped from around the site of a veld sore was noticeable in the cases seen in South Africa. The films and cultures made from the last examined vesicle showed characters identical with those of the first vesicle.

Thus a lesion has been produced from a remote culture of the coccus isolated from a veld sore, which resembles the initial lesion produced by inoculation with the original blister fluid of that case, and from the lesion the coccus has been recovered and cultivated, and found to exhibit characters identical with the original cultures.

Objection may perhaps be made to this experiment on the ground that the blistering of the epidermis was not sufficiently spreading. It seems, however, that this was unavoidable; indeed, had the inoculations completely failed, it would not have been a matter of surprise, since the clinical history of the sore shows the great rarity of the sore in healthy people. That on the healthy subject, despite a maximal infection on a skin burnt by long exposure to South African sun and wind, is feeble; how much less may any extensive lesion be expected on a protected healthy skin from a remote subculture!

The remoteness (fourteenth) of the subculture, and the fact that one generation had remained in an hermetically sealed tube for two months, are circumstances calculated to greatly affect the virulence of the coccus.

The histology of the veld sore.

I was permitted to remove portions of two veld sores occurring as fresh unopened blisters in "time-expired" men.

These were hardened in alcohol, embedded in paraffin, cut and mounted in the usual manner. Deep staining with Loeffler's methylene blue solution, and subsequent washing in 1 per cent. acetic acid, and a light wash of eosin, was found to give the best results. Gram's staining method is unsuitable, owing to the tenacity with which certain epithelial strata retain the stain.

In passing from the healthy epidermis to the diseased part, the first indication of the sore is a cleft in the stratum lucidum, which gradually widens into the cavity of the blisters. Beneath this cleft the cells of the stratum granulosum differ from the normal deeply staining cells by being glassy and swollen-looking. The whole thickness of the granular and Malpighian layers is twice that of the healthy portion. Passing from towards the centre of the sore, these layers become thinner, the regular wavy outline of the papillæ is lost, the base of the Malpighian layer is very irregular; in some places fairly deep processes extend into the dermis, and at others it is only two or three cells thick, and these cells are flattened. The epidermis is never wholly absent. The cells of the stratum lucidum and stratum granulosum become more swollen, and ultimately the layers are only represented by a few strands of badly staining cellular tissue, dotted over with leucocytes.

The raised stratum corneum is at the edge of the bleb, connected with the floor of the blister by a few strands of swollen cells; later it is quite free, but to its under surface adheres swollen badly staining fragments of cells and a few leucocytes.

The dermis shows only a very moderate degree of leucocytic invasion beneath the main area of the blister; there is little or none beneath the growing edge.

Starting from the recess forming the edge of the blister, it is noted that the split within the stratum lucidum, seen with the low power, extends for a yet greater distance, and that beyond this there is a tendency to a separation of the cells of the layer. The affected cells have a dirty yellow semi-opaque appearance, in contrast to the clear glossy look of the healthy cells. Around

and apparently within these discoloured cells are several cocci.

The surfaces of both roof and floor of the blister at its edge are covered with the same yellow cell stuff, which has assumed the appearance of granular *débris;* within this are masses of cocci.

As the epithelial layer thins off towards the centre of the floor of the sore, it is noticeable that in the upper layers of cells there is a marked distension of the intercellular spaces to form a network of cavities, and a vacuolation of the cells themselves. There are but few cocci within these spaces, but the cell meshwork swarms with them, whilst in the older parts of the sore numerous leucocytes adhere to the meshwork.

In this older region the remaining cells of the Malpighian layer are irregular in shape, and vacuoles appear both in and between the cells. The cocci do not penetrate to the cells.

Throughout the section and that removed from the other sore the cocci are everywhere disposed as diplococci, whether isolated, in chains, or in clusters of diplococci.

The tissue changes described are those assignable to an irritant working primarily within the epidermis, in that layer known as the stratum lucidum; the irritation is not severe, but of sufficient strength to cause destruction of epithelial cells and vesication.

It is not unreasonable to presume that the cocci found where these changes are seen are the cause of these changes. The cocci are not found in the healthy portions of the specimen.

The nature of the micro-organism found in the lesion.

A coccus has been found uniformly in, and has been isolated from the blister fluids in all cases of the sore examined: this coccus has been passed through numerous subcultures without any change of growth. Inoculation of man with the blister fluid, from a case where this coccus was in pure culture, has caused a characteristic sore, and from this sore the coccus was recovered after eight days, greatly increased in number, and in pure culture. Inoculation of man with a tenth subculture has in two cases set up only a local inflammatory reaction; in another inoculation two minute blisters appeared alongside the abrasion; in the latest inoculation with a fourteenth subculture,

the virulence of which had been intensified by growing in blood-mixed media, three vesicles arose, one of which reached the size of 4 × 3 mm. in three days. From these vesicles the coccus was recovered and cultivated.

These data fulfil the postulates of Koch, save for some lack of assurance afforded by the smallness of the bleb produced in the last-named experiment. Supposing this experiment to be considered sufficiently satisfactory, the case will be complete, this organism will be proved to be the cause of the veld sore.

As I have said before, should the inoculation experiments have completely failed, it would not have been a matter of surprise, for the clinical history of the sore has shown the rarity of the occurrence of the lesion in healthy people; further, a fourteenth subculture, one generation of which strain had remained in a sealed tube for two months, may be expected to have lost some of its pristine virulence.

As to the question of the nature of the organism, here there are two possible alternatives:

1. That it is an attenuated form of *Staphylococcus pyogenes aureus*.

2. That it is a special organism, which may be spoken of as *Micrococcus vesicans*. In favour of the latter view may be cited the following points:

(*a*) That the sore is quite different from any lesion at present recognised as a result of an infection by *S. p. aureus*.

(*b*) That the organism as seen in the sore, whether in film preparations of the fluid drawn therefrom or in sections, is always disposed as a diplococcus, even when in chains or clusters.

(*c*) That the growth of the organism in all media is from the outset more luxuriant than that of *S. p. aureus*.

(*d*) That the organism in the blister fluid and the subcultures thereof shows a resistance to destruction which is considerably greater than that exhibited by *S. p. aureus*.

(*e*) That in the unbroken blisters and in the experimental inoculations, although a considerable inflammatory reaction is present, no fluid that could be called "pus" is produced, the exudate is always serous, and that which contains the greatest number of the organism contains the smallest number of pus cells.

Against this view, and in favour of the organism being the *S. p. aureus* in an attenuated form, are the following arguments:

(*a*) That the occurrence of the coccus in the blister fluid as a diplococcus is not necessarily a diagnostic morphological feature, since diplococci occur in lesions that are known to be connected with *S. p. aureus.*

(*b*) That the general likeness of the cultures of this organism to those of *S. p. aureus* is strong; the organism undoubtedly shows greater luxuriance of growth, but breeds of *S. p. aureus* are known to differ.

(*c*) That although the sore is unlike any lesion known to be produced by *S. p. aureus*, yet on an analogy of the streptococcal lesions we might be led to expect some such lesion as possibly resulting from the action of an attenuated but resistent form of the staphylococcus. The streptococcus can produce, under varying circumstances, either general pyæmia, cellulitis, or an erysipelatous blush and vesication; so a series might be expected for the staphylococcus of pyæmia, local abscess, boils, pustules, and lastly, blebs of the epidermis, or "veld sores."

(*d*) That the climate conditions under which the veld sore appears is such that one might expect, by a process of survival of the fittest, the gaining of an increased resistance on the part of a facultative saprophyte and parasite, and the possibility of such a gain being counterbalanced by a diminution of pathogenic vigour.

The possibility of some such process occurring was further suggested by the comparative rarity of septic wounds on the high veld, and the marked difficulty often met with in cleansing a wound that had become septic.

This last view of attenuation, although not subject to proof,[1] was one which seemed very likely to me when in South Africa,

[1] Abbott (7), speaking of the most resisting colonies of *Staphylococcus pyogenes aureus*, which survived the action of mercuric chloride in a solution of 1-1000th for ten and twenty minutes, says the first generations, that is up to the seventh and eighth from the resisting colonies, are frequently incapable, when injected into the circulation of rabbits in the ordinary amounts of from 0·3 to 0·5 c.c. of the bouillon culture, of giving rise to the characteristic abscess formation in the kidneys and muscles which is seen to follow the injection of the same amount of a culture which had not previously been exposed to sublimate. After a ninth generation the organisms appear to gradually regain their virulence

and as such I suggested it in a note to the 'British Medical Journal' (4). But these last two suggestions may be put aside as possibly irrelevant.

There now remains to be considered whether or no the data in favour of the organism being a specific organism, the *Micrococcus vesicans*, are of sufficient weight.

From the consideration of the data afforded, it would appear that four points may be held sufficient to differentiate this organism from the *Staphylococcus pyogenes aureus*:

1. The distinctive features of the lesion.
2. The appearance of the organ uniformly as a diplococcus.
3. The greater luxuriance of the growth of the organism on nutrient media.
4. The greater resistance to destruction exhibited by the organism.

The "Natal Sore."

I was for some time in doubt whether the sore of this name, of which I had heard, was the same as the veld sore or not; indeed, many had such vague ideas on the subject that the names "veld sore" and "Natal sore" frequently passed for synonyms.

Happily I was able to get satisfactory evidence as to its nature from several Natal people, lay and medical, and to see it and examine it myself.

A long resident in Natal thus described the sore to me; the description as I noted it down so well gives the points of the sore that I transcribe my notes.

"The Natal sore starts as a small black spot (a black-head from a choked pore), then a yellow pustule forms, and the skin gets lifted up in a thick lump, which is red; it is like a soft, coreless boil. It occurs in places which are warm and moist, and have plenty of vegetable, animal, and human life. It occurs in towns, *e. g.* he had seen it in Pietermaritzburg. He had never seen it in the Transvaal or Orange River Colony high veld. He

until they are finally capable of producing those changes which follow constantly the injection into the circulation of normal organisms.

On the other hand, Smirnow (17) shows that attenuated cultures of the organisms of anthrax and swine erysipelas are much less resistent to destruction by germicides than are the normal organisms.

said it was not anything like the veld sore which he knew and had suffered from."

Two days after I had obtained this description I saw a specimen of an undamaged sore which I examined bacteriologically.

Corporal K—, 5th Lancers, fighting in South Africa fifteen months, just arrived in Cape Town from Natal, had a new sore of three days' growth on the dorsum of the hand. It seemed just like a boil, a purplish-red tumulus, capped with a yellow pustule about the size of a lentil. The sore was washed, the pustule opened with a sterile knife, and on squeezing the lump there exuded a large quantity of viscid, creamy pus. There was no "core" or slough. The red tumulus was now quite flabby, and its walls were found to be composed of both scarf and true skins, and beneath these a probe would pass freely in all directions for a space having a larger area than a shilling piece. The sore was cleansed with 1—1000 mercuric chloride solution; it healed rapidly.

A scar of another of these sores on the wrist showed characters similar to those of a healing boil, a livid colour with concentric rings of peeling epithelium around the depressed central point of perforation.

The film prepared from this case showed very numerous pus cells, streaks and networks of coagulated lymph, and numerous cocci disposed mainly in clusters, in a manner typical of *Staphylococcus pyogenes.*

The cultures showed, in twenty-four hours, white and pale yellow colonies which proved to be composed of cocci; later the colonies became nearly all yellow, but they never attained the rich colouring of the coccus of the veld sore.

LITERATURE.

Notes on the Veld Sore.

1. *Austen.*—'Brit. Med. Journ.,' Lond., 1901, vol. i, p. 486.
2. *Berne.*—Ibid., p. 1476.
3. *Harland.*—Ibid., p. 952.
4. *Harman.*—Ibid., p. 1266.
5. *Ogston.*—Ibid., p. 951.
6. *Pridmore.*—Ibid., p. 211.

7. *Abbott.*—"Corrosive Sublimate as a Disinfectant against *Staphylococcus pyogenes aureus,*" 'Johns Hopkins Hosp. Bull.,' Baltimore, 1891, vol. ii, p. 50.

8. *Smirnow.*—"Ueber das Wesen der Abschwachung pathogener Bacterien," 'Ztschr. f. Hyg.,' Leipzig, 1888, Bd. iv, S. 231.

25. *Fatty infiltration ("vacuolation") of the nucleus in fat-cells.* **De vacuolatione nuclei in cellulâ adiposâ.**

By S. G. Shattock.

Commentato diligenter mihi visum est eos maxime erasse qui non multo ante nostram ætatem linguam latinam adhibere, noluerunt ut medium quo ii qui in scientiâ naturali versantur inter se communicare possent.

Quorum quantus sit error omnes nunc vident quum numerus linguarum quibus utuntur ii qui de rebus naturalibus scribunt, maxime multiplicatur.

Ex quo fit ut nemo omnia de re qualibet scripta cognoscere possit quamvis accurati in catalogis sint descripta. Ad cujus rei remedium, nihil valet, ut mihi videtur, introducere aliam novam et non ante coguitam linguam quæ sit omnibus communis, quia omnes qui litteris humanioribus (ut dicuntur) operam dant, jam lingua latina utuntur; quinetiam ut pars disciplinæ superioris fere necessaria habetur.

Quæ si in eundem locum qua antea restitueretur, nullum eveniet detrimentum alicujus linguæ recentioris progressioni; in libris enim qui nonnisi de rebus puræ scientiæ tractant, nec expectatur talis progressio nec tentatur. Nam in re scientiæ modo postulatur expositio accurata rerum et legum quibus gubernantur, sine litterarum floribus aut ornamentis.

His igitur persuasus sententiis ausus sum hujus tractatus in linguam latinum redditum brevissimum proferre summarium, ut alii judicent quanta facilitate lingua illa ad res scientiæ naturalis exponendas, etiam nunc accomodari possit, et ut concitentur animi eorum qui cognoscere cupiunt ea quæ alii scripserunt de iisdem rebus quibus ipsi student.

Attamen si, forsan, minus conveniens videatur totum opus latine vertere, summarium saltem ejus utilissime edi posset ut ab hominibus cujusvis nationis intelligatur.

Summarium.

Vacuolationem nuclei in cellulâ adiposâ primus Sir Victor Horsley anno 1885 animadvertit. Phænomenon maxime com-

mune est in telâ adiposâ eorum qui myxœdemate ægrotant; in telâ adiposâ autem normali et in ea lipomatorum etiam animadvertitur. Ego pingue in linguæ linea media examinavi; fontem autem pinguis, credo, nullius esse momenti. Quia vacuolatio maxime distributa est, fieri posse putavi ut infiltratio cum oleo ejus causa esset, quod quidem verum fuit.

Vacuolum pene semper singulare est, nonnunquam duplex; immutatur magnitudine, quod primo perexiguum est, deinde parte reliqua nuclei majus fit.

Nunc de præparationibus tinctis (Sudan III et Hæmatoxylin) dicemus. Difficultas una dijudicationis ex hoc constat, quod si nuclei vacuolati desuper spectantur, vix possibile est judicare utrum color ruber vacuolo vere inhæreat, an sit in oleo quod in cellulâ continetur, atque per spatium intranucleare conspicitur.

Hoc dijudicare possumus ex studio nucleorum eorum qui se in margine cellulæ inveniuntur. Quum nucleus in ipso margine cellulæ jaceat, deformitas quam vacuolum efficit notabilissima est, cellula enim umbonem monstrat.

Quum sectionem opticam intuimur, olei guttula intranuclearis tincta colore rubro definiri videtur in latere profundiori reliquis nuclei attenuatis.

Hæc probant oleum in telâ adiposâ formanda, non modo in cellulæ corpore sed non raro etiam in nucleo ipso servari.

Sack ('Archiv für mikroscopische Anat.,' Band xlvi, 1895) demonstrare non potuit oleum in vacuolo intranucleari esse, sed, ut credo, hoc erroribus artis histologicæ attribuere oportet.

In solo exemplo ex quo in hanc conclusionem venit, tela adiposa in liquore acidi chromosmici (Flemming) submersa postea in paraffino infixa est. In preparationibus meis, tinctis Sudan III et Hæmatoxylin, et in glycerino conditis, sine usu alcohol ethylici aut xylol, dubitari non potest quin guttula intranuclearis ex oleo constet. Hæc, præterea, cum observatione scriptoris supra citati congruent, viz. vacuolum intranucleare in telâ adiposâ tabescente evanescere.

Vacuolation of the nuclei of fat-cells was noticed by Sir Victor Horsley in 1885, and is thus an observation of some standing.[1]

[1] An address "On the Physiology and Pathology of the Thyroid Gland," delivered before the Medical Society of London ('British Medical Journal,'

It is in myxœdema that the phenomenon has been more particularly described, Horsley's observation having been confirmed in this country by Professor Boyce and Mr. Beadles.

The observations of the two latter authors are recorded in the 'Journal of Pathology,' 1893: in skin from the side of the neck, in a case of myxœdema, they note that the nuclei of the fat-cells almost invariably presented a curious appearance owing to the presence of a larger or smaller vacuole; they record the same appearance in the subepicardial fat in sections of the heart.

The phenomenon is, however, by no means confined to the fat in this disease. Following Sack, Mr. Beadles[1] has described it in the subcutaneous fat from other cases, and in the fat of lipomata.

Nevertheless the proportion of cells exhibiting the change in such circumstances is not great. He remarks, "Very different is it in the case of myxœdematous patients, where amongst a group of fat-cells in a field of the microscope a number of vacuolated nuclei are invariably to be seen." Accompanying the paper is an illustration ('Trans. Path. Soc.,' vol. xlix, 1898, pl. viii, fig. 3), showing the change in question, in the interstitial fat of the myocardium.

The particular organ on which the observations to be noticed were made was the tongue of a West African negro, the material itself having been kindly obtained for me by Major W. Cooke Daniels; and my primary object had been to see how far the lyssa might be represented in the lower races of man.

In the tongue there was an incomplete median septum of adipose tissue, the cells of which presented very conspicuously the condition of nuclear vacuolation.

The source of the fat, however, is, I believe, immaterial. Are the contents of the vacuoles determinable? and if so, of what do they consist? Seeing that the condition is of such wide distribution in adipose tissue, the possibility which presented itself to my mind was that the nuclear vacuoles, like the body of the cell itself, held fat. Certain technical difficulties arose in testing this surmise, but after surmounting these its correct-

December, 1896, where the appearance is shown in a microphotograph accompanying the address, fig. 11).

[1] 'Trans. Path. Soc.,' vol. xlix, 1898.

ness was made clear. Of the two chief stains for fat, osmic acid and Sudan III, I selected the second, its great advantage being that the fat is dyed of a positive red colour, and nothing except the fat. Without a counterstain it is practically impossible to recognise the nuclei; for this I chose Ehrlich's hæmatoxylin.

The sections were cut on the freezing microtome, and stained for twenty-four hours in 80 per cent. alcoholic solution of Sudan III, after being passed through 95 per cent. alcohol; they were afterwards washed in 80 per cent. alcohol, and then transferred to Ehrlich's hæmatoxylin, washed in distilled water, then in tap water, and finally mounted in glycerine. The hæmatoxylin may be used indifferently before or after the Sudan III. The study should be carried out with $\frac{1}{12}$ oil immersion.

The vacuolation, as distinguished from the contents of the vacuole, is easily made out with $\frac{1}{6}$, in preparations stained with hæmatoxylin and mounted in Canada balsam after dehydration and clearing in the usual manner. The vacuole, which in such preparations it really is, is almost always single, but it may be double, and I have seen it triple. The cavity varies in size, being in the first stage quite minute, but when largest it exceeds the rest of the nucleus.

But to pass to the preparations stained with Sudan III and hæmatoxylin: one of the difficulties in the determination lies in this, that if the vacuolated nucleus is viewed on the flat it is almost impossible to decide whether the red coloration of the vacuole is intrinsic, or is the colour of the fatty contents of the cell appearing through the intra-nuclear space. Even when the fat-cell has been divided so that its contents have escaped the cell is coloured red, proving obviously that a layer of oil still adheres to the inner surface; and I have observed this to be so, moreover, in parts of cells into which air has entered. It is by the study of such nuclei as appear at the margin of the cell that the determination is to be made; and only a certain number of these are disposed in so favourable a way as to be of service.

In the case of the lesser vacuoles the difficulty presents itself of determining whether the fat droplet, stained red with the Sudan III, lies within the nucleus, or is displaced from without against it; for in all such preparations a certain number of

free droplets of oil occur from the division of the cells, and the escape and entanglement of their contents on the section.

In the case of the larger vacuoles the histological picture offers no ambiguity.

When the nucleus lies precisely at the edge, the most noticeable feature is the deformity occasioned by the vacuole, the cell presenting a marked protuberance or boss on its exterior; this deformity is obviously due to the tension within the body of the cell preventing protrusion from the deep aspect of the nucleus.

The contents of the vacuole as so viewed on an uncoloured background are fully stained red, and thus proved to be fat. The appearance is as though a hernial protrusion of the oil within the main body of the cell had taken place; and such a phenomenon is quite conceivable. That this is not what happens, however, is proved on reaching the true optical section of the nucleus, when the fat droplet is seen to be bounded on the deep side by the thinned remains of the nucleus itself. I have observed a gap, however, in this deep limitary line, but such is exceptional, and possibly secondary to an extreme distension. On focussing from the surface the part first defined is the semicircular edge of the flattened nucleus, for the vacuole in all cases is more or less central, the periphery of the nucleus retaining the flattened form proper in the case of the fat-cell. As the cell is penetrated the unaffected periphery of the nucleus disappears and the true optical section is reached: the droplet is then seen to be almost spherical, with its greater convexity outwards; it does not bulge towards the cell cavity, the tension within the cell preventing any encroachment on this aspect. At either side the intra-nuclear droplet is sharply bounded by the nuclear chromatin which rises up for a varying distance around it.

The prominent outer border of the droplet is sharply defined, and remains so at different levels, showing that it is contained within a limiting membrane prolonged over it; sometimes, too, the outline of the projecting part of the droplet is not mathematically regular, and in this resembles the outline of the cell as contrasted with that of a free droplet of oil.

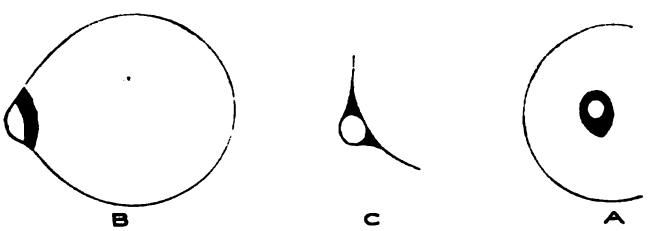
These observations make it clear that in the process of fatty infiltration of the cells in the formation of adipose tissue, oil is

stored not only in the body of the cell, but not infrequently in the nucleus as well.

There is no sign of any nuclear disintegration; the chromatic network remains normal and is merely displaced; the oil so stored is a single droplet, and this, again, relates the process to that of fatty infiltration as distinguished from one of degeneration. How far the process of mitosis would be affected by such an infiltration can only be guessed at; should it be called for, the oil would probably be first removed.

Arnold Sack[1] in his dissertation upon the subject of nuclear

FIG. 22.



A. The vacuolated nucleus of a fat-cell viewed on the flat.
B. The vacuolated nucleus of a fat-cell viewed from the side, showing the circumferential portion of the flattened nucleus; from the centre of the latter the fat droplet projects as a boss from the cell.
C. The same nucleus in optical section, showing the line of chromation between the fat droplet in the nucleus and the fat in the body of the cell. (Studied with $\frac{1}{12}$ oil immersion.)

EXPOSITIO FIGURÆ.

A. Nucleus vacuolatus cellulæ adiposæ desuper conspectus.
B. Nucleus vacuolatus cellulæ in latere conspectus. Monstratur margo nuclei compressi cujus ex parte media olei guttula exstat sicut umbo e cellulâ.
C. Nucleus idem in sectione optica conspectus.

vacuolation in fat, has missed the fact, perhaps, of chief interest, viz. that the contents of the vacuoles consist of oil. Sack's preparations in general were made by the celloidin and paraffin method of embedding, the final stages being completed in the usual way with absolute alcohol and clearing fluid.

The particular observation upon which he bases his generalisation that the nuclear vacuole of the fat-cell does not hold fat, was made by placing human fat immediately on its removal from the living body into Flemming's solution.

[1] 'Archiv für mikroscopische Anatomie,' Band xlvi, 1895.

In a foot-note the author draws attention to the well-known fact that osmic acid does not penetrate very deeply, so that it becomes essential to study the superficial parts of the tissue. To this may be added the difficulty of ensuring sufficient blackening, in the case of minute droplets of fat, to render their identification certain, and the fact that the tissue after treatment in bulk with Flemming's solution was embedded in paraffin before the sections were cut.

One must assume that the technique adopted by the author named was unreliable for the demonstration of the smaller droplets of oil.

In my own preparations, stained with Sudan III and mounted in glycerine without the use of absolute alcohol or clearing fluids, the coloration of the nuclear droplet is quite distinct, and the presence of fat placed beyond dispute.

This result, moreover, fully harmonises with Sack's own observations that in atrophic states of fat (in children or aged persons emaciated from disease) the nuclear vacuoles disappear; that the more pronounced the atrophy the smaller is the number of vacuolated nuclei; and that the vacuolation is only to be observed in well-developed adipose tissue.

So far from holding with Sack, therefore, that the nuclear vacuoles stand in no direct relation to the fat formation of the cell, I, on the contrary, conclude that the fatty infiltration of the nucleus is to be associated with that of the cell, and that the disappearance of the intra-nuclear fat must be related to the atrophy of the cell.

April 7th, 1903.

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26. *A specimen of mammary carcinoma which had been treated by X rays.*

De penitiori structurâ carcinomatis mammæ radiis "X" subjecti.

By S. G. Shattock.

Summarium.

Ægra multipara erat ætatis 50, in cujus mamma carcinoma durum animadversum est. Incepit curatio, die 23 Aprilis,

1902. Post viginti dies tumor se minuerat, atque super partes subjacentes paulum moblior factus est.

Excisa est mamma die 19 Augusti, anno eodem, curatione continuata fere usque ad diem excisionis.

Nunquam aut rubuit aut inflammata est cutis, quæ super mediam partem tumoris retracta est, ipsa autem non invasa.

Sectiones microscopicæ per totum tumorem scissæ demonstrant structuram penitiorem nullo modo mutatam esse. Stroma ejus carcinomatis duri aspectum communem ostendit. Nonnulli lymphocyti in eo sparguntur, præcipue circa marginem tumoris. Paucitas cellularum cum nucleis polymorphis insignis est. Præter lymphocytos cellulæ "mast" ut dicuntur, atque plasmacyti (Unna) inveniuntur.

Pars præcipua, *i. e.* epithelium, ex cellulis polymorphis constat, in ordinibus, ut solet, tenuibus ac flexuosis dispositis. Cellularum nuclei omnes recte tinguntur (hæmatoxylin), atque hic illic figuras mitoticas ostendunt: nec necrosis, nec cytolysis, nec phagocytosis apparet.

Degenerationis oleosæ vix ulla indicia adsunt (Sudan III). In nullo loco destitit margo tumoris extendere.

In sectionibus tinctis (Biondi-Ehrlich-Heidenhain) apparet in quibusdam cellulis structura a nonnullis scriptoribus corpus parasiticum habita. Arteriolæ aut in stromate tumoris aut in telâ adiposâ circumjacenti, integræ sunt.

Hæc ostendunt quam paulum efficiunt radii "X" quum agitur de neoplasmate profunde posito, atque cute defenso.

THE curative effects of the X rays upon rodent ulcer are now fully established, and this is equally true of other cutaneous forms of carcinoma, whether primary or metastatic.

Opportunities, moreover, have been taken by different observers of studying histologically the process of cure in the first-named lesion.

The X-ray dermatitis is something very visible, palpable, and indisputable.

When we come to the case of more deeply seated malignant tumours, screened from the action of the rays by the skin or mucous membrane, we enter upon a much more obscure subject, and one in connection with which further data are imperatively

required, not only such as come from clinical observation, but those also to be derived from histological investigation.

One source of hope rests in the possibility that the rays may induce a premature degeneration and necrosis of the more rapidly proliferating and less stable epithelium of the carcinomatous growth, to be followed by a phagocytic removal brought about by the more vigorous normal cells, *i. e.* that the healthy structures may remain intact under the same agency that may lead to the death of the abnormal.

But upon all such surmises the evidence of observation is wanting, and the present specimen may serve as the beginning of a study into this subject.

The specimen which I have had the opportunity of examining came from a patient shown by Mr. W. F. Brook at the meeting of the British Medical Association held at Manchester in July, 1902. The report of the case appears in the 'British Medical Journal,' Oct. 25th, 1902, p. 1305, under the heading Case 3, and is accompanied with a figure showing the condition before radiotherapy was commenced.

The patient was a multipara aged 50, in whom the menopause had occurred five years previously, and who noticed during November, 1901, a depression in the skin overlying a lump to the outer side of the right breast.

In April, 1902, the lump had increased and become painful, the pain extending down the inner side of the right arm. Three weeks later Mr. Brook saw the patient; at that time the skin over the outer margin of the right breast was puckered and bound to the lower border of the pectoral and to the intercostal muscles through the medium of a hard, ill-defined mass about two inches in diameter. X-ray treatment was commenced on April 23rd, with a daily exposure of ten minutes. In a week the pain was completely relieved. In three weeks the tumour had appreciably diminished in size, and had become slightly moveable. By the end of July, after fifty exposures, which were gradually increased to three quarters of an hour, the mass appeared to be half of its original size, and could be moved over the subjacent muscles through a maximum excursion of two inches in each direction. The treatment was continued to within a week of the removal, which was carried out on August 19th, 1902. At no time was any dermatitis induced.

The specimen as now preserved (Mus. Royal Coll. Surgeons, 4809 B) is a vertical section of the growth with the surrounding fat. The skin over the centre of the tumour is retracted, but without being infiltrated. The new growth measures in the section about 1·5 cm. ($\frac{3}{5}$ inch) in diameter vertically to the integument, and about 2 cm. ($\frac{4}{5}$ inch) in the opposite direction. Its margins are ill-defined and stellate from extensions into the mammary tissue and surrounding fat. Centrally it presents a fine opaque net of epithelium in the more translucent fibrous stroma, from which net prolongations are traceable into the more peripheral parts of the neoplasm.

The microscopic sections were made so as to include the whole of the tumour, and were studied after various methods of staining. The tumour is a spheroidal-celled carcinoma of the typical scirrhous type, the proportion of stroma exceeding that of the epithelium. To take the *Stroma* first; this consists of dense strands of fibre with flattened connective-tissue cells, and is of the typical hard type. Mingled with it there is a noteworthy amount of elastic tissue. This is not uniformly distributed, and though otherwise obvious it is brought into bold relief in sections stained for twenty-four hours in Unna's acid orceïn. Peripherally the stroma is continued into the fibrous trabeculæ of the surrounding fat, and into these the elastic tissue is also in places prolonged.

In the stroma there occurs a fair number of lymphocytes, but they are most irregularly distributed. In the central main part of the tumour the lymphocytic infiltration is absent. It is practically confined to the periphery, *i. e.* to the extending portion of the growth, but even here it varies capriciously without discernible reason. Both fat and connective tissue are in places abundantly infiltrated about the epithelial extensions, as well as in advance of them. In other situations both kinds of tissue are penetrated with epithelial ingrowths without presenting much or any infiltration.

The fewness of polymorphonuclear leucocytes is conspicuous. Mast cells occur in the stroma in moderate numbers, the densely crowded granules staining of a deep maroon in sections treated with polychrome blue and neutral orceïn.

Besides the lymphocytes and mast cells, here and there a group of plasma cells (Unna) lies in the stroma. Such cells

occur in conjunction with lymphocytes, and where close-set affect a mutually adapted polyhedral form. In certain of these cells the deeply staining nucleus is fragmented, the fragments being mostly coarse, of irregular shape, and moderate in numbers. Such cells have no other nucleus, and cannot thus be viewed as phagocytes engaged in the destruction of lymphocytes.

Epithelium.—Throughout the neoplasm the epithelium is arranged in the characteristic narrow meandering lines in the clefts of the stroma, its cells being of the polymorphous or spheroidal type.

Peripherally the narrow columns extend into the fibrous prolongations of the mammary stroma as well as between the individual vesicles of the fat.

The course of the epithelial advance is determined by the tissue clefts, and it is interesting to observe what ensues when the epithelium encounters the elastic tissue in its progress: the column of cells may become broken, and the elements dispersed,—entangled, as it were, in the dense web of elastic fibrils.

Throughout the section the epithelial nuclei stain normally, and in some of the alveoli they present mitotic figures. There is no cell necrosis. Some of the sections, cut on the freezing microtome from material fixed in formol, were stained for twenty-four hours with Sudan III in order to study the question of fatty degeneration. The stain demonstrates a notable absence of fatty degeneration anywhere in the carcinomatous epithelium.

This offers a marked contrast to what has taken place in the epithelium of the few glandular acini which persist about the marginal parts of the growth; most of the epithelial cells in these hold deep red minute droplets of oil; the columns of the larger-celled carcinomatous epithelium, even those in the close proximity of the acini, contain none whatever.

Doubtless the question will here arise, Is the "cancer body" present? This the Biondi-Ehrlich-Heidenhain stain displays in its typical forms and true colour; in some of the epithelial cells singly, pressing aside the cell nucleus: in others, in the characteristic groups.

To all this it must be added (as already noticed) that at the margin, on every side, the appearances are those of exten-

sion; narrow prolongations of the large-celled epithelium lie in the connective tissue and fat, without presenting any trace of degeneration.

Finally as to the arterioles. Both the larger of these in the fat immediately about the tumour, down to the smallest which lie in the midst of the fibrous stroma of the growth, are quite normal. There is no trace of recent endarteritis or sclerosis; nor were any encountered which had become blocked from an invasion of their wall by the neoplasm, after the manner described by Goldmann. Nothing of the nature of an arterio-sclerotic or other arterial form of atrophy of any areas of the growth is present.

I have entered into these details by reason of the important practical issues concerned in the radiotherapy of the more deeply seated malignant tumours. And if it is allowable to feel in a matter of pure observation, my own feeling is one of profound disappointment at so barren a result. For we have here a case in which treatment was followed, to all appearance, by a diminution in size of the mass, and its increased mobility over the subjacent structures. Nevertheless, although the treatment was continued to within a week of the excision, the histological study reveals no degeneration or lysis of epithelial cells; nowhere is a phagocytic invasion of epithelium in progress, and on every side the edge is as in an advancing condition; the "cancer-body" is intact, and mitosis is proceeding in the epithelial cells. As to the lymphocytes, they are not more numerous nor are their clusters denser than I have seen in scirrhous tumours of the breast, on which no treatment has been carried out before their excision; nor is there anything in the presence of mast cells and plasma cells not met with in carcinoma elsewhere, notably as pointed out by Unna in many carcinomata of the skin.

The clinical diminution in size and increased mobility of the mass cannot, as yet, be satisfactorily explained. Possibly they were due to the reduction of a subinflammatory œdema about the advancing periphery. I had put the question how far such a result might have been due to rest and immobilisation of the arm. But Mr. Brook, in answer, writes that such a factor may be eliminated, for not only was immobilisation not carried out in this or either of the other two cases he reported, but on the

contrary, as the shoulder became less fixed, the patient was encouraged to use it the more.

December 2nd, 1902.

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27. *The effect of X rays on rodent ulcer.*

By M. S. Mayou.

In studying the effects of X rays on tissues, the first question that arises is, What are X rays? As far as is at present known in an ordinary spectrum of light are ultra-violet rays, which are well known to be especially active on chemical agents. An electric spark is also extremely rich in these rays. Now when a spark is allowed to pass through a vacuum the rays coming from the kathode have the peculiar property of not being refrangible, and therefore their wave-length cannot be measured. According to Jackson these rays are very nearly allied to ultra-violet rays, and have different wave-lengths. When the X rays are allowed to fall on living tissue they produce an inflammation which is quite superficial. On the other hand, the rays by which photographs are taken penetrate the body deeply, and therefore are in all probability not of the same wave length as the rays which produce inflammation. Another argument in favour of this fact is that rays from the soft tubes which have least penetrating power produce most reaction in the superficial tissues. And lastly, tissues in the deeper parts of areas exposed to X rays show no changes. In X rays we have a form of energy which can be compared to mechanical, thermal, electrical, or chemical stimuli, which when applied to the body produces a superficial inflammation, but which has the peculiarity that its application is painless, and that its effects are more lasting. That it is painless may be due either to the fact that the application of this form of energy extends over such a long period that it does not produce any impression on the nerve endings owing to the stimulus being so slight, or that the nerve endings cannot appreciate its application, just as light produces no effect on the skin, whereas it is easily appreciated by means of the optic nerve.

It is now well known that the application of X rays will make all forms of rodent ulcer heal, and I hope to show to-night that this healing ought to be permanent.

The peculiarity of the inflammation produced by X rays is that it does not reach its full height until some time after the exposure, say in from one to three weeks. This inflammation is greatly increased and more rapidly brought about by simultaneously applying irritants. This point I want to emphasise and illustrate by one or two cases, as I think it is not generally noted. A man was sent to me to be X-rayed for a superficial epithelioma of the hand. After about two weeks' exposure it was thought to be increasing in size, so a local excision of the growth was performed. So much sloughing occurred that the arm had to be amputated above the elbow. Some time ago I had rather a severe X-ray burn on my hand, and I found that the least irritation, such as washing my hand, caused it to become hot, painful, and bright red, and after assisting at an operation, and putting my hands in 1 to 20 carbolic, was followed by extensive sloughing of the skin. This observation led me to use 1 in 20 carbolic acid for dressing rodent ulcers in the early stages of X-ray treatment whenever possible, and this I find has the double advantage of keeping them aseptic and of accelerating primary reaction.

This susceptibility to irritants, I think, can be largely accounted for by the vaso-motor paralysis which occurs in an inflamed part, and which, when more irritation is applied, leads to greater and more complete dilatation of the vessels. This dilatation of the vessels seems to be permanent at the seat of the most acute inflammation, for if a part be examined after recovery from an X-ray burn dilated vessels can be seen all over the area. This increased susceptibility to irritants is, I think, a most important factor in the healing of rodent ulcer, for it is largely due to the irritation produced by the rodent cells on the surrounding tissues that, I think, X rays have such a wonderful effect. Otherwise why should the new growth disintegrate and not the surrounding tissue?

By the application of X rays to a part we can produce an inflammation leading to anything from a mild leucocytosis to an actual gangrene. This is brought about, I think, in exactly the same way as an inflammation is produced by other forms of

stimuli, and is most severe at the point first struck, *i.e.* the superficial tissue.

In rodent ulcer the tissues are invaded by a new growth, which sets up a slight inflammation, and this in all probability is Nature's method of trying to rid herself of the disease. At the same time the growth is dependent on the underlying tissues for its nutrition. Now if we excite an acute inflammation the part furthest from the source of nutrition dies, and will come away as a slough. This will account for the disappearance of the large masses of nodular growth which so

FIG. 23.

Rodent ulcer; "healing stage." The upper part of the field shows a mass of the epithelial cells of the growth invaded by leucocytes; the lower part shows the degeneration of the epithelium which takes place before the invasion occurs. Zeiss, obj. D; oc. No. 4.

rapidly takes place under treatment. But if a section of rodent ulcer be examined, we find lying under apparently healthy skin cells of the growth. Now how is it that these cells disappear also, as they obviously cannot be thrown off as sloughs? If a section of rodent ulcer after it has just begun to react to X rays be examined, the clumps of epithelial cells which make up the growth are found surrounded by enormous numbers of leucocytes. We know it is the duty of these leucocytes to remove all irritating substances from the part by breaking

them up and carrying them away, or, failing that, to encapsule them with fibrous tissue, shut off their nutrition, and so prevent their spread. In a section of rodent ulcer which has nearly healed we find a mass of granulation tissue organising, with healthy epithelium growing in from the edge. Scattered here and there amongst the infiltration of leucocytes are epithelial cells of the growth in various stages of degeneration. The degeneration seems to take place from without inwards towards the centre of the clumps of epithelial cells, which become

FIG. 24.

Showing the histology of a rodent ulcer which has healed. The epithelium of the skin has spread over the surface of the ulcer. The fibrous stroma of the growth remains, and the spaces which previously contained the epithelial cells of the neoplasm are now filled with masses of leucocytes, together with a few degenerate cells. Obj. 2 inch; oc. No. 2.

vacuolated. The granules in the cells increase in numbers, collect around the cell wall, and seem in places to be making their way through it, and disappear. The nuclei do not as a rule proliferate, although there are some large cells with multiple nuclei to be seen, which are probably derived from the stroma. The chromatin filaments cease gradually to take up the stain until nothing but the cell body remains, which is apparently removed by the leucocytes.

In treating a rodent ulcer I find it most useful to remove

portions of the growth from time to time to ascertain whether there are any active cells of the growth present, and if they have all disappeared to cease treatment.

December 2nd, 1902.

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28. *Fibromatosis of the nerves of the tongue [Macroglossia neurofibromatosa], and of certain of the nerves of the head and neck.*

(With Plates I, II.)

De Macroglossiâ neurofibromatosâ.

(Cum Tabulis I, II.)

By F. C. Abbott and S. G. Shattock.

Summarium.

Hoc titulo designamus macroglossiæ varietatem adhuc non descriptam. Qui morbus repertus est in puella quattuor annorum. Lingua tumida fere semper ex ore exstabat sed retrahi potuit. Modo pars sinistra membri aucta est. Tumebant etiam papillæ fungiformes, vesiculæ autem nullæ aderant. Tumida erat pars faciei sinistra sed tumor imperfecte circumscriptus, ac ad erubescendum proclivis fuit, puellâ mente concitata. Nulla sudatio ruborem consequitur. Ad hæc accedit quod in hoc latere nullum crinium incrementum apparuit.

Pars anterior dimidii sinistri membri amputata est atque per incisionem longam in sinistro latere cervicis excisus est tumor nervis maxime crassis compositus, una cum glandulæ submaxillaris parte superficiali. Parte linguæ, quæ excisa erat, dissecta, inveniuntur omnes nervi crassi atque longitudine aucti ita ut plexum compactum forment. Quum pars excisa e posteriori examinetur, tela muscularis vix discerni potest propter crassitudinem nervorum qui in ea jacent.

Scrutatio microscopicus demonstrat partem maximam sectionis ex nervis crassis constare, inter quos fasciculi musculares late sparguntur. Linguæ incrementum solum morbo nervorum

efficitur, telis interjacientibus compressis sine aut lymph- aut hæm-angeiectase. Crassitudo nervorum etiam in papillis apparet.

Hanc crassitudinem tela fibrosa, quæ ab endoneurio formatur, efficit. Vagina laminata nervum quemque amplectitur. Nervi tumidi e cervice excisi similiter mutantur. Læsio quidem linguæ ejusdem generis est ut pachydermia sive elephantiasis neurofibromatosa cutis.

ALTHOUGH neurofibromatosis or plexiform fibroma of nerve is a well-recognised disease, the examples which fall under individual observation are few. In certain situations it is, relatively speaking, not uncommon; but the part most strikingly involved in the present instance, viz. the tongue, is so rare, and the disease so unique in degree, that we are led to report the case in detail. Clinically the condition of the tongue falls within the category of macroglossia, but it has nothing in common with the ordinary lymph- or hæm-angeiomatous form of that disease; and should it be included hereafter under the general name of macroglossia, it will need differentiating by such a term as that suggested in the title of the present communication.

Clinical account and clinical remarks. By Mr. ABBOTT.

D. Q—, a female child four years of age, was admitted into St. Thomas's Hospital in August, 1900.

She was the youngest of a family of seven, of whom three others are living and healthy, and three died in infancy.

There is no family history of deformity or tumour except that a new growth was removed from the cheek in the case of a first cousin of the father.

The swelling of the tongue was first definitely noticed by the doctor who vaccinated her when two months old. The mother, however, thinks the tongue was not quite normal when the child was born. She is sure that the peculiar formation of the ear was present at birth; and that when the baby cried, the ear and side of the face down to the mouth used to flush and become quite red, as, to a certain extent, they still do.

The tongue steadily increased in size, and when the child was one and a half years old began to protrude from the mouth, which has been more and more constantly kept open with the tongue exposed.

From this time the increase has been steady, and with it the now-nearly-always protruded tongue has curled at its tip upwards and to the right. Its surface has been dry, but never very troublesome, and the only sore has been one on the frænum, due to pressure from the lower incisor teeth.

The teeth and alveoli have given no trouble, and dentition has been regular.

The child began to talk at the usual age, but speech has been indistinct from the first, though it has got worse *pari passu* with the enlargement of the tongue. Latterly, for some months before admission, the tongue has been almost constantly protruded from the mouth, even during sleep. She has, however, a way of curling it backward, and, as it were, swallowing it into the roof of her mouth, which can then be entirely closed.

The mother has thought but little of the fulness of the left side of the face, and cannot say when the swelling in the neck began to be marked, but thinks it has "gradually increased with the rest."

Allowing for the general increase in size, the deformity of the ear is much as it was at birth, though there has been gradual increase in the thickening.

State on admission, August, 1900.—A bright country child, well developed both physically and mentally. The tongue is greatly enlarged, and is kept throughout the day, and nearly always also when asleep, widely protruded from the mouth. It can, however, be withdrawn within the teeth and the mouth closed on it, but the child is not so comfortable in this state. This withdrawal is managed by a peculiar rolling movement upward and to the right, aided by the head being thrown backward, as if she were swallowing a pill.

On closer examination the enlargement of the tongue is seen to involve only the left side of the organ, and to be strictly limited by the median raphe. The enlargement is in all three directions—length, breath, and thickness. The right half is stretched out along the raphe, appearing narrower

than normal. Owing to the tension of this, the raphe forms a bow-curve with concavity to the right, and apparently ends on the right side of the organ some way behind the greatly enlarged tip, the whole of which is formed by the left half of the tongue.

The thick tip is also curved sharply upward, so that behind it there is a deep concavity on the dorsum, bounded by the thickened free edge of the left side of the tongue. Behind this concavity comes a convexity due to the local pro-

FIG. 25.

Showing the condition of the protruding tongue, as described in the text.

Lingua tumida ex ore exstans monstratur. In uno loco papillæ insigniter eminent. Vesiculæ nusquam adsunt.

minence described below. The enlargement of the left side extends back as far as, possibly even further than, the circumvallate papillæ. Its consistence is tough and firm, and on pinching it the feel is coarsely granular. Posteriorly there is a fairly circumscribed "tumour," shaped like a flat almond, with its long axis forward and outward. This "tumour" is about an inch in length, and extends from the median raphe to the left border of the tongue.

It reaches nearly back to the circumvallate papillæ, and about two thirds of it are generally protruded from the mouth. It is most plainly circumscribed on the dorsal surface, and it is in the mucous membrane covering it that the changes in the fungiform papillæ are especially conspicuous. The mucous membrane covering the tongue is dry, thickened, and opaque,

FIG. 26.

Showing the protruding tongue and want of symmetry of the face due to the diffuse swelling of the left side of the latter.

Incrementum monstratur linguæ et partis sinistræ faciei, crassitudine nervorum effectum.

forming dull white patches in places. The dryness is not extreme, and the general appearance is one of coarsening. There are some deep folds along the free edge, and extending downward from it.

On the dorsum the whole surface looks coarse and granular,

this change being more marked posteriorly, especially over the local prominence due to the circumscribed tumours (Fig. 25). This appearance is due to a very marked enlargement, both in diameter and height, of the fungiform papillæ, which form conspicuous objects. They are paler than normal, owing to the thickened corium over them.

Fig. 27.

Showing the protruding tongue and diffuse enlargement of the left side of the face and neck, in profile.

Lingua tumida, una cum tumore partis sinistræ faciei ac cervicis monstratur.

Clinically the conical papillæ also appeared enlarged, but possibly this was only due to the general thickening of the corium. No vesicles, containing either clear fluid or blood, could be seen on any part of the surface. The palate and fauces were quite normal. The face presented a vague diffuse fulness

of the whole of the left side, partially obliterating the natural lines, and diminishing the expression on this side. The mucous membrane of the lips showed a similar unilateral thickening, but to a very slight degree. This fulness extended over the ramus of the jaw, and became much more marked in the submaxillary triangle and upper part of the neck. Here it formed a conspicuous swelling, extending from the mid-line back to the anterior border of the sterno-mastoid, and down to the level of the hyoid bone. Whereas on the face no structures could be made out in the swelling, in the neck it consisted of masses of lumps and knotted cords, plainly to be felt through the skin.

FIG. 28.

Showing the swelling of the helix of the left auricle described in the text.
Auricula sinistra; tumor, crassitudine nervorum, forsitan, effectus ex helici exstans monstratur.

The left ear presented in a marked degree similar changes to those in the face. It looked obviously larger and thicker built than its fellow, and its long axis was increased by half an inch. The thickening involved the whole rim of the helix, and the lower part of the antihelix and antitragus. It was, however, most marked in the extension of the forepart of the helix across the cavity of the concha, which cavity was nearly filled up by a smooth mass like the pulp of a finger.

These enlargements all seemed to be of the skin and not of the cartilage, and the skin on the posterior surface of pinna was also coarse.

The child was very conscious of the badness of her speech before strangers. Her words were thick and badly formed, but it was quite possible to understand what she said. She was mentally quick, and very bright in disposition.

Saliva dribbled from the angles of the mouth, especially during sleep, when the tongue was kept protruded, and she snored loudly. There was no difficulty in taking ordinary food, and the hearing was not affected by the malformation of the auricle.

Owing to the youth of the patient, it was found impossible to test the taste on the affected side. Whenever the child cried, or got into a temper, a definite, bright, unilateral flush suffused the whole left side of the face. This the mother had noticed from early infancy. It was not, as far as we could observe, accompanied by unilateral sweating.

First operation, September 5th, 1900.—Under chloroform, a V-shaped portion, consisting of the anterior two thirds of the left half of the tongue, was excised. The posterior incision was planned to fit against the cut surface of the raphe. No portion of the right side was removed. A small portion of the posterior part of the circumscribed growth was certainly left behind, and from this we believe the present recurrence to have commenced.

The circumvallate papillæ were not removed. The corium was thick and tough. The tongue substance was firm and bled but little, and the cut surface showed numerous coiled, partially opaque white cords, between and also among the muscles. The cut surface left behind on the left side showed a similar structure. There was an entire absence of the capillary oozing that is usual in ordinary macroglossia. The two cut surfaces were sutured together to form the new tongue, which now pointed to the left side and lay entirely within the mouth.

The temperature remained quite normal after the operation, and all was soundly healed when the stitches were removed on the ninth day. Within a fortnight she could talk again, and the power of articulation was much as before operation.

Second operation, September 26th, 1900.—With the object of reducing the swelling beneath the jaw, a large curved incision was made from the mid-line back to the anterior border of the

sterno-mastoid, extending as low as the hyoid bone. The flap was dissected up and a curious condition exposed. The swelling consisted of coils of semi-transparent white cords, inextricably twisted with swollen knots in places. These cords varied much in size, from thread-like ones to others the size of a No. 3 catheter.

The condition invaded all the anatomical structures of the part, and rendered their differentiation difficult. The two bellies of the digastric were made out and found involved. This tissue was cleared entirely from the submaxillary triangle, the removal including the superficial part of the submaxillary salivary gland and lymphatic glands. Posteriorly the removal was carried some way behind the ascending ramus of the jaw. There was again very little bleeding, and the wound was entirely closed.

After this operation the swelling of the left side of the face increased, and facial paralysis was noticed on the second day, complete below but not above.

The stitches were removed on the seventh day. The temperature throughout was normal. A considerable quantity of clear serum was let out from the wound at the dressing and several times afterwards, till it entirely closed on the sixteenth day. Massage of the cheek was begun a few days after operation, but did not materially reduce the swelling. The facial paralysis gradually became more obvious.

Dr. Turney, who kindly examined the child in the electrical department, made the following reports:

October 11th.—"Left facial nerve. No reaction to faradic current. To galvanic current no reaction either, but this was not carried far for fear of upsetting the child."

November 1st.—"No faradic irritability in either division of the left facial. It must be remembered, however, that it is impossible to use stray currents. At all events there is no sign of repair so far."

The child left hospital on November 9th with a small battery to be used at home. The tongue lay entirely in the mouth and was nearly symmetrical, and articulation was quite as good as before operation. The appearance of the neck was greatly improved, but the facial paralysis with the fulness of the left side of the face still rendered her very unsightly. She was not

seen again by us till the summer of this present year. Her health in the meantime had been good. Some power had returned in the face, the improvement being most marked in the last month, and her articulation had much improved. The face had remained full for a considerable time, but this condition had also latterly much improved. The return of the lump in the tongue was first noticed in the summer of 1901. On the whole this gradually gets larger. She never snores at night now.

Condition on May 6th, 1902.—The tongue lies entirely in the mouth, which is naturally kept shut. It moves freely and is fairly symmetrical. The raphe still passes over somewhat to the left, but has largely resumed its median position. There is a recurrence of the tumour formation the size of a small almond. This has evidently arisen from the portion of the circumscribed formation left behind at the first operation. The mucous membrane over this portion presents the same characters, with the enlarged papillæ, as before. There is no trace of enlargement on the right side.

Several attempts were made to test the taste, but failed on account of the youth of the patient. Tactile sensation was apparently normal.

The swelling of the face that occurred after the operation on the neck has entirely disappeared, and the face presents again the slight general fulness on the left side as at first.

The unilateral flushings when she cries still take place, but are somewhat less marked.

The facial paralysis has much improved. The left eye can be shut and even be partially screwed up, and is normally closed during sleep.

The actual nerve condition was reported on by Dr. Turney: —"Left facial nerve. Orbicularis oculi acts well. Orbicularis oris requires strong currents, but contraction is quite distinct. Taking into account the long history, however, I should consider any further improvement doubtful, but it is quite possible."

The ear is much as when last seen, but the thickening has slightly increased.

There is no return of the knotted tortuous cords in the area of operation on the neck, but they can be easily felt around this area, and extend in various directions. On careful exami-

nation enlarged nerve-cords can be felt in, and as far as, the following positions:

(1) Close to the mid-line of the neck in front of the sterno-mastoid muscle.

(2) Down to the second piece of the sternum.

(3) Over the whole area of the posterior triangle and crossing the clavicle.

(4) Beneath the skin over the mastoid process, and above and behind the pinna.

In no instance do they cross the mid-line of the body, even in the tongue and submaxillary region.

From a clinical standpoint the case was a puzzle, and the true condition was not even suspected till after operation and the pathological examination of the parts removed. The tongue itself closely resembled the condition in cases of the tough fibrous form of macroglossia of lymphatic origin. The special features were the strict limitation to one side of the organ, and the more circumscribed tumour, in addition to the diffuse new formation.

Besides these were the marked enlargement of the fungiform papillæ and the entire absence of any signs of dilated lymph or blood spaces. Almost the only clinical feature to excite suspicion in the tongue itself was its granular feel and the cord-like structures in its substance. The smooth solid thickening of the face and ear was explained as due to congenital blocking of the lymphatics of the face and neck, while the nodular and cord-like masses in this latter situation were thought to be maldevelopments of the same system.

These formed the most unusual clinical feature of the case, and should in a similar one lead to a correct diagnosis of the true pathological condition.

The clinical condition in the neck exactly resembled that described in neuro-fibromatosis, and of which one of us has a vivid remembrance in the case of diffuse neuro-fibroma of thigh described in another part of this paper.

In that case, also, covering the definite masses of neuro-fibroma was a smooth thickening of the skin and subcutaneous tissue as was present in our case, in its true characters representing a diffuse molluscum fibrosum, and corresponding to the multiple soft fibromata of Recklinghausen's disease. Was the

general thickening of the side of the face and the enlargement of the ear of similar origin? Both Mr. Shattock and I believe this to be the correct explanation, and it would best account for the inequalities of its distribution, and the almost localised tumour made by this condition across the concha of the ear. It is true that no changes in the nerve-cords of this area could be felt, but neither can they be in Recklinghausen's disease.

Another possible explanation must be borne in mind—the possibility of the thickening being due to some trophic change, and connected with the unilateral flushings and vaso-motor disturbance acting from infancy and possibly from fœtal life. We do not see how to explain these flushings except as due to some implication of the cervical sympathetic.

This nerve may very probably have been involved with the others on this side of the neck, but the explanation needs the further large assumption that the diffuse neuro-fibroma causes interference with nerve function, of which there is no proof in the case of motor or sensory nerves, certainly none in the present case. With this explanation in view the child was examined for unilateral sweating, for changes in the pupil or vessels of the fundus, and for abnormal growth of hair, but in every instance with a negative result. Nor would this theory harmonize with the almost local tumour formation in the ear, and we discard it for our other hypothesis.

The facial paralysis which resulted immediately from the second operation was no doubt due to the plexiform fibroma removed having been largely of the facial nerve after it had broken up into its main divisions. It must have been impossible from the incision made to reach the normal course of the branches of the temporo-facial. But so tortuous does the dissection prove the nerves to have become that many of these branches may have looped down in their course, and so have been divided.

The extent of the paralysis that followed the operation is confirmation of the wide involvement of the facial nerve, even to its upper branches.

From the condition seen at the operations, the examination of the parts removed, and the recent re-examination of the patient, the following nerves appear to be those involved in the fibromatosis, viz.:

Motor.—The hypoglossal, facial, and motor branch of the third division of the fifth nerve.

Sensory.—The glossopharyngeal nerve, lingual and auriculo-temporal branches of the third division of the fifth, and probably the first and second divisions in addition. The transverse cervical, supra-sternal, and supra-clavicular descending branches of the cervical plexus, the small occipital, and probably the great auricular as well.

Sympathetic.—The sympathetic was possibly involved on the left side, as indicated by the unilateral flushings mentioned above, but no other proof of this was found.

Pathological description and pathological remarks by
Mr. SHATTOCK.

The specimen exhibited and figured is the left half of the tongue, showing, in a highly pronounced degree, the condition of fibromatosis of the nerves, or plexiform fibroma. Every nerve, as shown in the dissection, is enlarged from the disease, even to those terminating in the divided mucosa along the lower side of the organ. The nerve most enlarged, the trunk of the lingual, measures ·5 cm. in diameter. All the nerves are markedly increased in length as well as in thickness, so as to lie in serpentine or short transverse folds, with the result that in many situations a compact plexus has been produced. Towards the middle line of the organ such a plexus quite conceals the distal portion of the enlarged trunk already referred to. In the divided posterior surface the muscular substance is hardly recognisable, by reason of the universal enlargement of the nerves lying in it.

The papillæ are increased in size, so as to give the surface an abnormally coarse appearance; this is especially marked over the posterior part in the situation of the chief swelling which is such as to render the general dorsum concave in place of convex. Some of the fungiform series measure as much as 3 mm. in horizontal diameter. The morbid condition did not extend into the right half of the organ, and the same asymmetry was apparent in the neck, the right side of which was free of disease, whilst in the left there were extensive neuro-fibromatous swellings to be later detailed.

Histology.—Sections carried transversely through the base of the portion of the tongue removed show that the enlarged nerves constitute by far the chief part of the sectional area, the bundles of muscle-fibre being widely disparted between them.

The enlargement of the tongue is due solely to the lesion of the nerves, the intervening muscular and connective tissues being compressed without trace of œdema or of lymph- or hæm-angeiectasis. The nerves are enlarged throughout the section, even in the conical and fungiform papillæ, and present in places figures of abnormal complexity due to the unnatural tortuosity brought about by their elongation.

The increase is the result of a diffuse formation of connective tissue, of loose or open texture peripherally, but of closer centrally, where the enlarged nerve presents a denser core in which here and there a medullated nerve-fibre is recognisable. Each of the enlarged nerves is circumscribed by a lamellar sheath or perineurium. The looser new-formed fibrous tissue is resolvable into ill-defined bundles of delicate wavy fibres, which subdivide to fill the intervening space with a widely open irregular mesh of finer fibres or single fibrils, and the tissue is provided with a considerable number of corpuscles of the ordinary connective kind. In cross-section the bundles appear naturally as collections of polyhedral points like those of the endoneurium, from which the new tissue has obviously arisen. In certain of the enlargements nerve-cells are present, *i. e.* spheroidal cells of large size with deeply stained violet body (hæmatoxylin and eosin), and a spherical nucleus of conspicuous size holding a well-pronounced nucleolus. Here and there such nerve-cells occur closely set in small groups within the enlarged nerve, each cell being provided with a multinuclear sheath. Some such cells lie in the nerves of the mucosa, others in those deeply placed.

The occurrence of these cells may be taken as proving the involvement of the glosso-pharyngeal nerve (in addition to the lingual and hypoglossal), since microscopic ganglia normally exist upon the expansions of this nerve in the human subject.

Transverse sections of the enlarged trunk of the lingual display a like diffuse formation of endoneurial tissue, which has disparted the still recognisable medullated nerve-fibres in its

DESCRIPTION OF PLATE I.

Illustrating the communication by Mr. F. C. Abbott and Mr. S. G. Shattock on "Macroglossia Neurofibromatosa." (P. 231.)

The upper figure shows the portion of tongue excised. The nerves in the surface divided at the operation have been minutely dissected. They are all thickened, elongated, and tortuous, so as to form a close plexus, which is prolonged into the muscular substance. The chief nerve-trunk is that of the lingual.

The lower figure reproduces a dissection of the chief mass of nerves removed from the neck; they have undergone the same general enlargement as those of the tongue. Near the middle of the picture is a considerable portion of the submaxillary salivary gland, the nerves of which are involved in the change.

TABULA I.

Ad dissertationem de "Macroglossiâ Neurofibromatosâ" illustrandam.

F. C. Abbott; S. G. Shattock. (P. 231.)

Figura superior partem linguæ amputatam ostendit. Nervi, minute dissecti, omnes crassi atque tortuosi sunt ita ut plexum compactum forment, qui plexus per telam muscularem pertendit. Truncus nervi princeps est lingualis.

Figura inferior dissectionem tumoris e cervice excisi repræsentat. Hic constat ex nervis maxime crassis ut illi qui per linguam pertendunt. Pars superficialis glandulæ submaxillaris, una cum nervis excisa, morbo affecta est.

From Photo.

Huth, Lith^r. London.

DESCRIPTION OF PLATE II.

Illustrating the communication by Mr. F. C. Abbott and Mr. S. G. Shattock on "Macroglossia Neurofibromatosa." (P. 231.)

FIG. 1.—A microscopic section of the substance of the tongue near the surface, showing the enlarged, fibromatous nerves, lying between and separating the muscular fasciculi. (2-inch obj.)

FIG. 2.—A section through the papillary part of the tongue, showing the enlargement of the nerves, one of which lies in the substance of a fungiform papilla. (2-inch obj.)

FIG. 3.—A section through the superficial part of a tongue affected with the common form of macroglossia, showing dilatation of the lymph spaces in the connective tissue of the corium and papillæ. (2-inch obj.)

FIG. 4.—A section of the thickened corium with the enlarged fibromatous nerves lying in it, from the case of neuro-fibromatous pachydermia described in the text. The nerves are enlarged as in the tongue of the child with which the communication deals; the tissue between the nerves is of the same kind as that of a soft fibroma, and as that which has led to the thickening of the nerves themselves. (2-inch obj.)

(From drawings by Danielsson.)

TABULA II.

Ad dissertationem de "Macroglossiâ Neurofibromatosâ" illustrandam.

F. C. Abbott; S. G. Shattock. (P. 231.)

FIG. 1.—Sectio microscopica linguæ, crassos, fibromatosos nervos inter fasciculos musculares interjacentes ostendens.

FIG. 2.—Sectio microscopica per partem papillarem linguæ perscissa. Monstratur crassitudo omnium nervorum, quorum unus in papillâ fungiformi jacet.

FIG. 3.—Sectio microscopica linguæ varietate macroglossiæ vulgari affectæ. Monstratur dilatatio canalium lymphæ in telâ cellulosa papillarum atque corii subjacentis.

FIG. 4.—Sectio microscopica cutis pachydermiâ neurofibromatosâ affectæ. Nervi crassi sunt ut illi in lingua puellæ in hac dissertatione descripta. Tela cellulosa inter nervos jaciens structuram fibromatis mollusci, sicut nervi ipsi, ostendit.

[illegible]

[illegible] Mr. [illegible]

[illegible]

[illegible]

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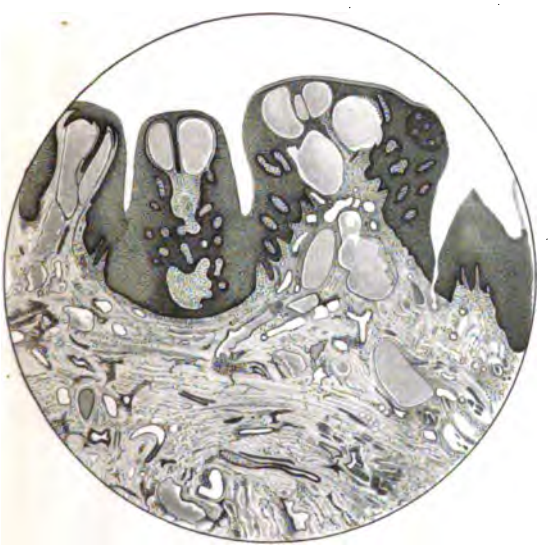
1.

2.



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midst. The cross-section offers no sharply circumscribed funiculi, but is irregularly and incompletely parted into areas of no regular form by ill-defined septa of connective tissue and vessels.

Sections of the tongue stained with Unna's acid orceïn show no trace of elastic fibre in the new intra-neural formation of connective tissue, though delicate elastic fibrils are mingled with the tissue of the mucosal corium, and the connective tissue elsewhere.

With the left half of the tongue there was removed, in two pieces, a mass from the left side of the neck. Each of these pieces admits, on dissection, of being resolved into a plexus of enlarged, elongated, and tortuous nerves. In connection with the larger (lower) of the two a considerable part of the superficial portion of the submaxillary gland was removed, together with a small extent of the platysma muscle. The nerves over the platysma, like all the rest, are thickened and tortuous, those distributed to it ramifying like gnarled roots amongst its fasciculi. The submaxillary gland is intimately connected with the diseased nerves, many of which penetrate it, and render its lobules unnaturally firm in consistence.

The upper of the two masses from the neck has precisely the same general characters, and it likewise comprises a small portion of the submaxillary gland, which, as a whole, appears abnormal in volume—a result to be ascribed to the enlargement of the nerves which pass through or supply it.

Microscopic examination of the gland reveals the fact that the pertaining nerves are as universally involved as those of the tongue. To describe one lobule: there is a periphery of normal gland tissue of varying thickness, but at certain spots defective from the displacement due to the thickening of nerves in the peripheral part of its substance; by far the chief proportion of the section consists of a plexus of fibromatous nerves, each of which is ensheathed with lamellar connective tissue, the entire area being resolvable into a mosaic of circular or oval foci, between which a duct here and there intervenes. The lamellar sheath is more prominent and relatively thicker than in the nerves of the tongue, in consequence of a more open condition of its lamellæ; whence it results that the division between the more central proper longitudinal elements of the nerve and the

circumferential is less sharply defined, and that the contiguous nerves are less clearly insulated.

Although the terms plexiform neuroma and neuro-fibromatosis are applied to the condition in question, the first is not strictly accurate, and is not adopted in this communication, since it is now generally allowed that no new formation of nerve-tissue is concerned in the production of the enlargement. The more accurate terminology would be plexiform fibroma of nerve. There are two examples of plexiform fibroma in the museum of St. Thomas's Hospital, both dissected and

FIG. 29.

Showing part of one of the lobules of the submaxillary gland involved in the fibromatous condition of the nerves. Obj. 2 inches.

Sectio microscopica unius lobuli glandulæ submaxillaris, quæ glandula ablata est una cum tumore nervorum e cervice exciso. Monstratur crassitudo nervorum intra glandulam jacentium.

examined at different times by one of us. The lesser of these is a small collection of elongated tortuous fibromata, which grew in the course of certain cutaneous nerves over the front of the left clavicle and the thoracic wall below and external to the right mamma. The case was that of a girl thirteen years of age operated upon by Mr. W. Edmunds in St. Thomas's Home in 1896.

The other is a typically constituted plexiform tumour about

four and a half inches in the longest direction, which was removed with the overlying integument from the inner side of the right thigh. In two situations the enlarged nerves are closely packed into a conglomerate mass about two inches in horizontal and one in vertical diameter, from which offsets run into the subcutaneous tissue, which is here thickened and condensed. The surface over the two masses is raised in corresponding somewhat prominent elevations, the disease in its entirety coming within the class of neuro-fibromatous elephantiasis or neuro-fibromatous pachydermatocele.

The patient was a woman 21 years of age, who was operated upon by Mr. Clutton, April 8th, 1896. The nodules felt in the enlargement before removal were excessively tender; and at the operation the thickened nerves were found to extend into and between all the muscles on the inner side of the thigh, as well as along the ischial and pubic rami. She was readmitted, July 18th, 1900, with a history of recurrence of pain about a year after the operation. Examination disclosed a few tender scattered nodules in the thigh, and a tumour in the left arm, which had been noticed six months. On July 27th an oval fibroma an inch and a half in chief diameter was excised from the arm, in connection with the median nerve, the funiculi of which were exposed at the operation. From the obturator region, together with some of the fat, there was removed a fibroma related to the obturator nerve. In this case an operation had been performed in the situation last mentioned when the patient was twelve years of age.

The larger nerves present the usual increase of connective tissue in which medullated fibres are recognisable. The thickening of the skin and the appertaining subjacent conglomerate of enlarged nerves are together so like what is present in the tongue (with which this communication is concerned) that they may be noticed in more detail. Histologically the skin presents a normal contour, and its papillary layer has the usual structure of coarse, close-set, interlacing bundles of fibrous tissue. A very short way beneath the surface, however, the fibrous bundles become abnormally disparted by a highly cellular connective-tissue growth, the fibre of which contrasts by its greater delicacy with that of the corium. Still more deeply the whole of the tissue is of new formation

must form the basis of any pathology of the pancreas, and certain of them are of direct pathological interest. It has long been known that a flow of pancreatic juice is excited at some time after a meal, namely, at a period when food or chyme passes from the stomach into the small intestine. Pawlow[1] has shown that this flow occurs only on the entry of gastric contents into the duodenum, and is specially determined by the acidity of these contents, a secretion of pancreatic juice being always obtained when a solution of dilute acid (·4 per cent. HCl) is introduced, either directly or through the stomach, into the duodenum. This observer has also shown the existence of a nervous mechanism regulating the opening of the pyloric sphincter, of such a nature that the sphincter remains closed so long as the contents of the duodenum are acid, but opens directly these are neutralised. Hence a small portion of chyme injected into the duodenum will evoke a flow of alkaline pancreatic juice, which will go on until the chyme is neutralised. Directly this happens the pylorus will open again, and a new portion of acid chyme enter the duodenum to evoke a fresh secretion of pancreatic juice. Pawlow ascribes this secretion of pancreatic juice to a nervous reflex from the mucous membrane by the central nervous system and vagus to the pancreas. Popielski[2] and Wertheimer[3] have shown that a secretion is obtained with equal success when all connections of the pancreas and duodenum with the central nervous system are destroyed, and therefore make the local ganglia of the pancreas responsible for the secretion.

Bayliss and I[4] have shown, however, that the mechanism is not nervous at all, but chemical. The mucous membrane of the duodenum, and of the rest of the small intestine to an extent, diminishing as the ileo-cæcal valve is approached, contains a body *pro-secretin*. Under the influence of acid this is hydrolysed and a body split off, which we have called *secretin*. This body is at once absorbed from the epithelial cells into the blood system, and passes to the pancreas, where it acts as a specific

[1] 'The Work of the Digestive Glands' (translated by Thompson), Griffin, London, 1902.

[2] 'Gazette clinique de Botkin' (Russ.), 1900.

[3] 'Journ. de Physiologie,' iii, p. 335, 1901.

[4] 'Journ. of Physiol.,' vol. xxviii, No. 5, 1902.

stimulus for the secretion. *Secretin* can be obtained by treating the mucous membrane of the upper part of the intestine of any animal with dilute acid, and if some of the solution thus obtained, freed from its proteids, be injected into the blood-stream, a flow of pancreatic juice is at once obtained.

A repetition of some of Pawlow's experiments on the influence of nerves on the pancreas has led us to believe that this chemical mechanism I have just described is the only mechanism for the stimulation of the pancreas, and that all the effects obtained by Pawlow on stimulation of nerves were probably due to a contraction of the stomach wall, and the ejection of its acid contents into the duodenum.

We thus have in secretin a means of exciting pancreatic activity at any time. And the fact that this body is identical throughout the whole range of vertebrates enables us to apply a secretin obtained from an animal's intestines to the stimulation of the pancreatic secretion in man.

Positive results have indeed been obtained in one case at the London Hospital by subcutaneous injection of secretin in a man the subject of a pancreatic fistula, and this procedure may serve as a useful diagnostic means in future in doubtful cases of the same nature. Since diabetes appears to be connected in some way with the pancreas, we thought it possible that some effect might be produced on the disease by intra-venous injection of solutions of secretin. This hope, however, proved to be unfounded, Dr. Spriggs having tried the intra-venous injection of secretin in a case of diabetes without producing any effect whatever on the course of the disease.

Our knowledge of the digestive functions of the pancreatic juice has been derived chiefly from the study of pancreatic extracts, and in Pawlow's earlier experiments on the pancreatic juice obtained from a fistula the juice was found to possess the three digestive powers with which this fluid has always been accredited, namely, on proteids, fats, and carbohydrates. More lately a pupil of his, Chepowalnikoff,[1] has called attention to the fact that, in the juice obtained from such a fistula, the greater part of the trypsin is present in the form of a precursor, trypsinogen, and that the full tryptic activity of the juice is evoked only when it comes into contact with the succus entericus.

[1] 'Thèse,' St. Pétersbourg, 1899. See also Pawlow, loc. cit., p. 159.

This secretion contains a body, *enterokinase*, called by Pawlow the "ferment of ferments," since its action is to convert trypsinogen into trypsin. It has been since shown by Delezenne[1] that, if the juice be obtained by a cannula in the duct itself without any contact with intestinal mucous membrane, it is perfectly inert on coagulated proteids, and we have shown that it has only a feeble proteolytic power on uncoagulated proteids such as fibrin or caseinogen. We thus see that the juice, which as secreted is practically inert on the proteid constituents of the tissues, becomes, on mixture with the succus entericus, the most potent proteolytic agent with which we are acquainted, digesting fibrin within ten minutes, and hurrying it rapidly on to the ultimate stages of disintegration (amido-acids, hexone bases, etc.). It seems possible that the accidental entry of the succus entericus into the gland through an abnormally dilated duct might account for the production of certain cases of pancreatitis. This condition has been produced in animals by injection of bile or of intestinal contents into the duct. We have sought to test this suggestion by experiment. In two experiments a solution of enterokinase was injected into the pancreatic duct, which was then ligatured, but without producing definite results. It is possible, however, that a repetition of this experiment with ligature of *both* ducts of the pancreas might be attended with more deleterious effects on the gland. At any rate, it is important to remember that the pancreatic juice will have very little corrosive and digestive action on the gland cells, unless by some means it can be contaminated with the succus entericus, a mere admixture of bile being useless for this purpose.

The most interesting outcome of these recent investigations is the light that is thrown on the ordered march of events in the alimentary canal. The satisfaction of appetite excites reflexly, through the central nervous system, the flow of gastric juice. The entry of the acid chyme into the duodenum causes the production of secretin in the epithelial cells of the mucous membrane. This is absorbed into the blood, carried to the pancreas, and excites the flow of alkaline pancreatic juice, which must cease as soon as the chyme is neutralised and the production of secretin stopped. At this point, however, the pylorus will open again, and fresh portions of chyme enter the

[1] 'C. R. Soc. de Biologie,' 1902.

duodenum until the stomach is empty. The pancreatic juice, which is inert on proteids, on coming in contact with the intestinal mucous membrane, excites a flow of succus entericus containing a ferment, enterokinase, which is necessary for the activation of the pancreatic juice. Once activated the trypsin exerts a violent proteolytic activity on the foodstuffs, but at the same time rapidly undergoes auto-destruction, so that at the lower end of the gut the intestinal contents are found to contain very little proteolytic ferment. The excoriation and irritation of the lower part of the bowel and anus, which may occur in cases of diarrhœa, may owe their production to the hurrying on of the active juice from the higher portions of the small intestine.

In view of the accurate adaptation which exists between the functions and activity of each section of the alimentary canal, it is not surprising that an external interference with these functions, such as a stimulation of the pancreas produced by abnormal means, and not from the intestinal wall, should result in a serious disturbance of the whole mechanism. And such is found to be the case. The secretion of pancreatic juice is normally evoked by the presence of acid chyme in the intestine. When we inject secretin intra-venously a large amount of strongly alkaline pancreatic juice is made to flow into the intestine. Here it meets with no acid to neutralise it, but still excites the secretion of succus entericus, which renders it an active proteolytic agent.

The result of this entry of strongly alkaline pancreatic juice into empty gut is to cause acute inflammation of the whole small intestine, an inflammation which is due to the pancreatic juice itself, and not to any direct effects of the secretin injected. Thus, in one of our experiments, two dogs of the same size were anæsthetised in the same manner. In one animal (*a*) a cannula was placed in the larger pancreatic duct, and the smaller upper duct was ligatured. In the other (*b*) the pancreas was left intact. In both animals repeated doses of secretin were injected intra-venously during a period of four hours. After three hours dog *b* suffered from diarrhœa, the liquid motions being tinged with blood. Dog *a* was still in good condition. At the end of four hours both were killed, and it was found that, whereas the intestine of *a* was perfectly

normal in appearance, the mucous membrane of the whole small intestine of *b* was deeply injected, with small, capillary hæmorrhages in the mucous membrane, and effusion of blood on the surface. [The intestines from the two dogs were shown at the meeting.] A similar condition of erosion caused by a reflux of the juice, and leading to the production of gastric ulcer, has been observed in toads which have received repeated injections of secretin.

At present we can only regard this experiment as a warning in any possible therapeutic use of secretin. If we desire to evoke from without increased activity of the pancreas, it will be essential to give our injections shortly after a meal, at a time when there is a plentiful supply of acid chyme, which can pass from stomach to intestine, to neutralise the alkaline pancreatic juice which will be secreted. Whether any cases of enteritis in man have a similar causation to that just described must be left to further investigation. At present the main lesson to learn from our experiments is the intimate coaptation of the various functions of the alimentary canal, and the danger of interfering with these by other than natural means.

It is certain, however, that in dealing with a given pathological condition in any part of the alimentary apparatus we must not direct our attention to this part alone, but attempt to trace back the processes in the ordered march of events which I have indicated above, and to discover in what stage of the process, and how far back, the disturbing factor has entered.

December 16*th*, 1902.

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30. *The influence of salts on the action of immune hæmolysins.*

By William Bulloch.

Hæmolysis is the exit of hæmoglobin from the red blood-corpuscles, so that the fluid in which they are suspended becomes of a red, transparent, "laky" colour. Ordinarily the corpuscles remain intact in salt solutions, the osmotic pressure of which is the same as that of the serum and the contents of the corpuscles

themselves. Such solutions are called "isotonic." It is not, however, possible in all cases to obtain isotonic solutions. With any strength of ammonium chloride solution, *e. g.*, hæmolysis promptly ensues, and for almost all salts there are limits below which laking occurs, such limits being spoken of as hypotonic.

Besides hypotonic solutions a large number of hæmolytic substances occur which act irrespective of any question of tonicity. As examples of this class may be mentioned certain glucosidal substances like digitalin, cyclamin, and the various sapotoxins.

A third group of hæmolysins differs from the preceding in the fact that the substances in question combine with the blood-corpuscles chemically, and behave like true toxins, resembling the latter in the fact that they give rise to specific antibodies.

These toxin-like hæmolysins are derivatives of both the vegetable and the animal kingdoms.

Among the toxic hæmolysins of vegetable origin are certain phytotoxins, such as crotin and phallin, which are intensely destructive to the erythrocytes. Others, such as ricin, robin, abrin, without producing actual hæmolysis, are capable of agglutinating red blood-corpuscles. Then comes the important though recently discovered group of bacterial hæmolysins, these being substances produced during the growth of bacteria in artificial culture-media. The most important of these are tetanolysin (Ehrlich-Madsen, 1), choleralysin, colilysin (Kraus and Clairmont, 2), staphylolysin (Neisser-Wechsberg, 3), pyocyanolysin (Bulloch-Hunter, 4), megatheriolysin (Todd, 5).

To the animal hæmolysins belong cobralysin (Stephens and Myers, 6; Flexner-Noguchi, 7; Kyes-Sachs, 8), phrynolysin or toad-hæmolysin (Pröscher, 9), arachnolysin or spider-hæmolysin (Sachs, 10), and the bee-lysin (Langer, 11). The most important hæmolysins of animal origin are, however, those contained in the serum. This may occur naturally, and the serum of one animal may produce *in vitro* and *in vivo* hæmolysis of the blood-corpuscles of another animal. From the classic researches of Bordet and Ehrlich, and Morgenroth, it is also known that such hæmolysins can be produced by the injection of erythrocytes of one animal into another of a different species. It is also common knowledge that these immune hæmolysins are complex in so far that the laking of the corpuscles takes place from the combined

action of two substances, the one commonly called the amboceptor, which is produced as a result of the blood injection, the other the complement pre-existing in the serum. Neither substance by itself can produce hæmolysis.

The experiments about to be detailed deal entirely with hæmolysins of this immune class, and were prepared by injecting rabbits with the blood-corpuscles of the ox.

Before, however, detailing these experiments I should like to refer to the structure of the mammalian red blood-discs. A great deal of doubt exists in regard to the finer structure of erythrocytes. Doubts have even been expressed on the question of their vitality. Certain it is, however, that by substances which produce laking, the so-called "shadows" of the corpuscles are left behind after the exclusion of the hæmoglobin. These shadows possess the form of the original corpuscle, and were regarded by Rollett as representing a stroma. Ehrlich (12) describes it as discoplasm, and regards it as the chief living portion of the erythrocyte, and as essentially a membrane which hinders the diffusion of the hæmoglobin. If in any way the life of the discoplasm is destroyed the hæmoglobin or paraplasm diffuses into the menstruum in which the corpuscles are suspended, and laking takes place. It may be taken as correct that the erythrocyte possesses two main elements—the stroma or discoplasm, and the hæmoglobin; and Bordet (13) and Nolf (14) have shown that the substances which give rise to the amboceptors are present in the stroma and not in the hæmoglobin. Sachs has also shown that the arachnolysin unites with the stroma just as with the intact erythrocyte.

The preparation of hæmoglobin-free stroma in quantity is a matter of difficulty, and different corpuscles vary much in this respect. For some corpuscles the method of Bordet is applicable. It consists in collecting the corpuscles, laking with distilled water, and then adding sufficient sodium chloride to make the whole solution isotonic. On centrifugalising the mixture the stroma sinks to the bottom of the tubes while the hæmoglobin floats above. Sachs has modified this method with advantage by heating the washed corpuscles to 54°—60° C. before laking with distilled water. By this method it is possible to get a good booty from the blood-corpuscles of the ox. I have worked out a method which I think gives more certain results with ox

stroma, both in regard to the quantity obtained and also in regard to the production of hæmolysin. The defibrinated blood is centrifugalised, and the corpuscles thoroughly washed with ·85 per cent. sodium chloride. To the mass of corpuscles eight to ten times the bulk of distilled water is added, and then about one fifth to one sixth of absolute ether. The mixture is then shaken in a separator, and in a short time the stroma rises to the top with the ether, the deeply coloured hæmoglobin solution remaining below, when it is easily run off. The ether-containing stroma is then mixed with saline solution and centrifugalised, when the stroma sinks to the bottom as a yellowish-white mass, and it is then collected by pipetting off the ether. It may be washed several times in ·85 per cent. saline, so as to completely free it from ether and traces of hæmoglobin.

When injected in small quantity into a rabbit this stroma produces powerful hæmolysins in the serum. It also combines *in vitro* with the amboceptors. Chemically the stroma is composed of nucleo-proteid, along with small quantities of lecithin and cholesterin. As prepared in the above way the stroma is very stable. One sample was dried over sulphuric acid, and was then powdered in a mortar, and kept in a cotton-wool plugged test-tube for six months. At the end of that time its injection provoked the formation of hæmolysins.

Experiments were made to determine which substance in the stroma it is that gives rise to the amboceptor formation. A quantity of hæmolysin-producing stroma was extracted for six hours in a Soxhlet's apparatus. At the end of that time the residue was incapable of producing a hæmolytic serum. The extract was also incapable, neither could I by mixing the residue and the evaporated extract produce hæmolysin. I therefore conclude that the nucleo-proteid it is which is the chief agent concerned in the production of hæmolysin, and that it loses this property if subjected to prolonged treatment with ether. In the short exposure to ether during the preparation of the stroma the nucleo-proteid is probably only slightly injured, but not enough to prevent its stimulating the cells to amboceptor formation.

Coming to the question of the influence of salts on the action of immune hæmolysins, very little work has been published. Markl (15) has shown that certain salts inhibit the action of

As an example of the first class, none better could be given than that recorded in the Society's 'Transactions,' vol. xxxix, 1888, by Dr. Joseph Griffiths; and, as still further simulating a plexiform fibroma, it arose in the neck. The tumour formed a large nodulated swelling, reaching from the mastoid process nearly to the sternal end of the sterno-mastoid muscle. The Morbid Growths Committee (to whom the specimen was referred) confirm the author's opinion as to the intra-vascular localisation of the growth, and add that, whilst this relation is obvious with respect to the greater part of the tumour, careful dissection shows that the large solid mass in the neck, extending between the muscular fibres of the upper third of the left sterno-mastoid muscle, is constituted by a plexus of veins enormously distended with similar new growth, and that what appear in the macroscopic section as lobes are in reality closely packed and distended veins; in some places the growth has for long distances no connection with the vessel wall, in others delicate adhesions exist, and in others again the growth is inseparably incorporated with the wall of the vein. The Committee observes that it is not improbable that by means of secondary adhesions arising between the advancing growth and the vessel wall the tumour may have received an accession in its blood-supply.

The heart and lungs had been removed in the ordinary way; nothing was found by Dr. Griffiths in the superior vena cava or the right auricle, but in the cavity of the right ventricle was a cluster of stunted shrub-like growths, apparently loose in the cavity, entangled in fibrin. Extending along the pulmonary artery was a slender irregular growth, 1 to 2 mm. in thickness, and a like growth lay in each division of the pulmonary artery and partially filled some of its branches. The extensions of the tumour within the pulmonary artery and heart were markedly cystic or tubular.

The testicle, however, is the organ from which intra-vascular growths so often arise, that they might at first be thought peculiar to this seat of origin.

Into the histological structure of these growths, and the various views held as to their nature, it is beside the present subject to enter.

In regard to the tumour from the neck before referred to, I have

had, through Dr. Griffiths's kindness, the opportunity of preparing and studying sections of one of the smaller veins (·5 cm. diameter) occupied by the growth.

The structure is so destitute of proper syncytium that the tumour cannot be satisfactorily placed in Schlagenhaufer's category of teratomatous chorional epithelioma ('Wiener klin. Wochenschrift,' Nos. 22, 23, 1902).

And finally, as an example of the opposite kind, I might adduce a plexiform fibroma which was removed by Mr. W. H. Battle, and parts of which I had the opportunity of examining ('Lancet,' vol. ii, 1896, p. 175).

The case was one of neuro-fibromatous pachydermatocele of the outer side of the right thigh, in a girl eighteen years of age. The thickened skin hung in large heavy folds. The mass was excised, and when dissecting up the deeper attachments a number of firm, white, moniliform and compound neuro-fibromata appeared. Sections of certain of these diseased nerves show the lax connective tissue already described; in the centre is a denser, more compact core with more numerous nuclei, in which lie medullated fibres: at its periphery the core merges into the looser connective tissue of the enlargement by a simple process of endoneurial overgrowth. The whole is limited by a lamellar sheath, from which the separation of the enlarged nerve occurs so readily that for half or more of its circumference there is, in some cross-sections, a continuous cleft between the two.

The resemblances, however, between plexiform intravascular tumours and plexiform neuro-fibroma are, it will be obvious, rather of a macro- than a microscopic character.

October 21*st*, 1902.

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29. *On some pathological aspects of recent work on the pancreas.*

By Ernest H. Starling, F.R.S.

Although the investigations I wish to describe have been carried out chiefly from a physiological standpoint, their results

ble to demonstrate the complemental action by gradually diminishing the quantity of magnesium sulphate by diluting it with sodium chloride of isotonic strength, showing that a certain quantity of magnesium sulphate is necessary for the inhibiting action.

We thus see that the action of immune body and complement varies much according to the medium in which the corpuscles are suspended, and that certain substances such as magnesium salts inhibit the hæmolytic action by preventing the junction of the complement with the immune body.

References.

1. *Madsen.*—"Ueber Tetanolysin," 'Zeitschr. für Hygiene,' 1899, xxxii.
2. *Kraus und Clairmont.*—"Ueber Hämolysine und Anti-hämolysine," 'Wiener klin. Wochenschr.,' 1900.
3. *Neisser und Wechsberg.*—"Ueber das Staphylotoxin," 'Zeitschr. für Hygiene,' 1901, xxxvi, p. 299.
4. *Bulloch und Hunter.*—"Ueber Pyocyanolysin," 'Centralbl. für Bakteriologie,' 1900, xxviii, p. 865.
5. *Todd.*—"Experimental Hæmoglobinuria caused by a Bacterial Toxine," 'Lancet,' 1901.
6. *Stephens and Myers.*—"The Action of Cobra Poison on the Blood," 'Journ. of Path. and Bact.,' 1898, v.
7. *Flexner and Noguchi.*—"Snake Venom in relation to Hæmolysis, etc.," 'Journ. of Exp. Med.,' 1902, vi.
8. *Kyes und Sachs.*—"Zur Kenntniss der Cobragift activirenden Substanzen," 'Berliner klin. Wochenschrift,' 1903, Nos. 2—4.
9. *Proescher.*—"Zur Kenntniss des Crotengiftes," 'Hofmeister's Beiträge zur chem. Phys. und Path.,' 1902, i, p. 575.
10. *Sachs.*—"Zur Kenntniss des Kreuzspinnengiftes," 'Hofmeister's Beiträge zur chem. Phys. und Path.,' 1902, ii, p. 125.
11. *Langer.*—"Untersuchungen über das Bienengift," 'Arch. intern. de Pharmacodynamie,' 1899, vi.
12. *Ehrlich.*—"Zur Physiologie und Pathologie der Blutscheiben," 'Charité-Annalen,' 1885, x.
13. *Bordet.*—"Les sérums hémolytiques," 'Annales de l'Inst. Pasteur,' 1900, xiv, p. 257.
14. *Nolf.*—"Contribution à l'étude des sérums antihématiques," 'Annales de l'Inst. Pasteur,' 1900, xiv, p. 297.
15. *Markl.*—"Ueber Hemmung der Hämolyse durch Salze," 'Zeitschr. f. Hygiene,' 1902, xxxix.
16. *Ehrlich und Sachs.*—"Ueber den Mechanismus der Amboceptorenwirkung," 'Berl. klin. Wochenschr.,' 1902, No. 21.

April 21st, 1903.

31. *On the relation existing between uric acid excretion and the breaking down of the white corpuscles.*[1]

By O. K. WILLIAMSON.

THE important fact that uric acid can, under certain conditions, be experimentally produced from the white blood-corpuscles was first observed by Horbaczewski (1). Following his research the relation of uric acid excretion to leucocytosis has been worked at by many writers from the clinical standpoint; among these Kühnau (2) and Richter (3) in Germany, Douglas (4) in this country, Zarnier (5), Giagmis (6), and Reale (7) in Italy may be mentioned.

If it be true that uric acid is formed from the white corpuscles, the fact is to be explained by its production from the nuclein contained in these cells, either as a result of their destruction or in consequence of their metabolism.

The conclusions arrived at by the above-mentioned observers have, when definite, been by no means in agreement.

Kühnau, in an extensive and careful research, showed that, following the crisis of lobar pneumonia, at which period there is an increased destruction of the white cells, there is an increase in the daily amount of uric acid excreted.

Making observations in various other diseases he found that following a decrease in the leucocyte count there is in most cases a corresponding increase in the daily amount of excretion of uric acid, an increase which he considers is caused by the increase in destruction of the white blood-corpuscles. He further showed that in leucocythæmia, in which condition the number of white cells in the blood is largely increased, the daily excretion of uric acid is also markedly increased.

With regard to his observations showing a rise in the amount of excretion of uric acid following a fall in the leucocyte curve, I would point out that the latter may be referable not to an increased destruction of leucocytes, but simply to a diminished production. As regards his researches in leucocythæmia,

[1] A thesis read at Cambridge in June, 1902, for the degree of M.D.

Milroy (8) and Malcolm have shown that in medullary as well as in lymphatic leukæmia, and Hale White and Hopkins (9) have demonstrated that in medullary leukæmia, the daily amount of excretion of phosphoric acid is diminished, so that the increased amount of uric acid excreted in these diseases can hardly be ascribed to an increase in the breaking down of the white corpuscles.

The other observers mentioned (with the exception of Richter, who lays stress on the importance of making observations extending over a considerable period of time) contented themselves with making in each case at most two or three observations on consecutive days of the numbers of white cells in the blood, and comparing these with the amounts of uric acid excreted on the same days.

Now, inasmuch as the physiological amount of daily excretion of uric acid varies for different individuals within wide limits (between ·2 and 1·5 grammes), it is obvious that the amount excreted in a particular individual under pathological conditions may be very largely increased without this amount exceeding these limits. It would seem to follow from this that observations of the ratio between the average amount of daily excretion of uric acid, and the average number of white corpuscles in the blood in a particular case, are of less value than consecutive observations in the same case, showing alterations in the one side by side with alterations in the other.

It must be confessed that, apart from Horbaczewski's experimental work, the only convincing observations as to uric acid being formed from the white blood-corpuscles are those of Kühnau on pneumonia.

My object in making the observations which are recorded below has been to determine, in pathological conditions, the times in each case observed at which an increased destruction of white cells is taking place, and to notice whether this is followed by an increase in the amount of daily excretion of uric acid. With this end in view daily observations were made of the number of white corpuscles in the blood for many consecutive days, whilst corresponding daily estimations of the total amount of uric acid excreted in the urine in twenty-four hours were also performed.

It is fairly obvious that, in any condition, such as advanced

pulmonary tuberculosis, in which there is a leucocytosis for a considerable period of time, there must be associated with this (always assuming that the leucocytes concerned are not specially long-lived forms) an increase in the amount of daily destruction of the white cells. When I refer below to increased destruction (as evidenced by certain alterations in the differential count to be presently explained) it must be understood that I mean an increase in the amount of destruction of the white cells over and above what has just previously been taking place (*i. e.* a relative increase in breaking down of the white blood-corpuscles). In order to prove that a rise in the amount of uric acid excreted is due to an increase in the destruction of the white cells, it is necessary to show a corresponding rise in the amount of phosphoric acid excreted; accordingly, besides daily observations of the amount of uric acid excreted, estimations of the daily amount of excretion of phosphoric acid were also made. As Milroy and Malcolm say, "it is hardly likely that there is a marked retention of the phosphoric acid in the organism; and if there be not, then the absence of the rise in the phosphorus excretion negatives the view that the alloxur bodies are derived from the direct breaking down of the nucleins."

Now an increased destruction of the white cells means a diminution in the number of the old cells, the young cells either not diminishing at all, or at any rate not to a corresponding degree.

Inasmuch as the polymorphonuclear neutrophiles[1] form by far the larger proportion of the white blood-corpuscles in a healthy individual, and are those concerned in ordinary leucocytosis, we will first consider them. Ehrlich's (12) view that the myelocyte and polymorphonuclear neutrophile represent different stages in the life history of one variety of cell, the myelocyte being the young cell, is generally accepted as correct. It is further probable that the small lymphocyte is quite distinct from these, being from first to last a small lymphocyte and nothing else, and that the large lymphocyte is like the myelocyte a young form of the polymorphonuclear neutrophile, about whose origin, however, we know less than in the case of the myelocyte. In examining a stained blood film from a case in which there is or has recently been a leucocytosis, forms intermediate in appear-

[1] In this article I have adopted the classification of Cabot (10).

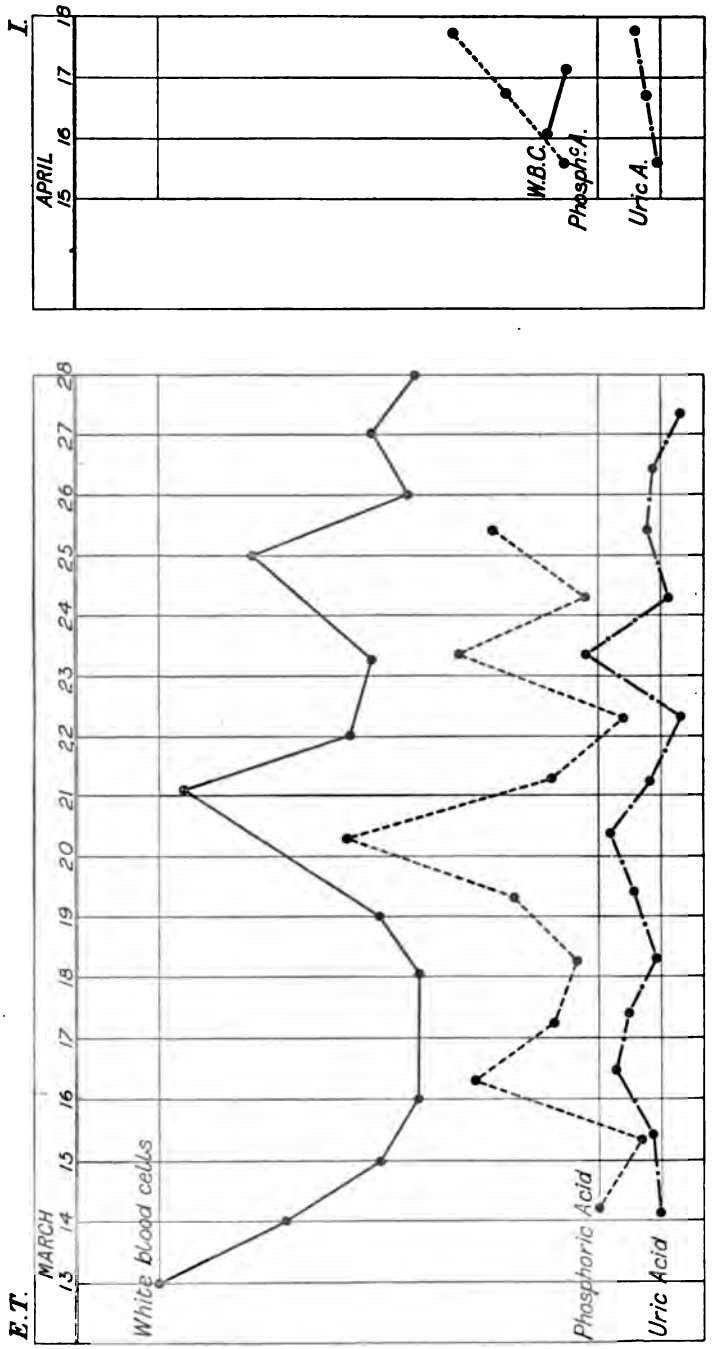
ance between the myelocyte and the polymorphonuclear neutrophile are to be seen in varying numbers. The nucleus of one of these cells stains evenly and lightly; it is circular or oval, or sometimes bilobed as if about to undergo division; moreover at times not only the nucleus, but the whole cell body is bilobed; the granules of the cell are similar to those of the polymorphonuclear neutrophile. Since all transition stages between the myelocyte and the polymorphonuclear neutrophile are represented by these cells, it is clear that they are intermediate in age between these two varieties, or are, in other words, simply young polymorphonuclear neutrophiles. Now if it be found, as the result of observations made on two successive days, that the polymorphonuclear neutrophiles are diminished in absolute number, the "young cells" (including the myelocytes) not being diminished, or at any rate not being diminished to a corresponding degree, it may be assumed that a destruction of this form of white corpuscle has taken place. If, on the other hand, these show that whilst there has been a diminution in the absolute number of polymorphonuclear neutrophiles the number of the "young cells" is also markedly lessened, an increase in destruction of this variety of cell cannot be assumed, but rather a diminished production. In order to determine the absolute numbers of each variety of white corpuscle, stained films were prepared, and differential counts were made from specimens taken at the same time as those specimens from which the simple blood-counts were made. By means of these differential counts one is thus able to obtain confirmatory evidence of breaking down of the white blood-corpuscles. As regards the small lymphocytes, inasmuch as we are unable to distinguish the young from the old forms of these, an increased destruction of this variety of cell can only be inferred when there is a fall in the number thereof, followed by a rise in the amount of excretion of phosphoric acid.

From an examination of the results it will be seen that in seventeen out of twenty instances in which an increased excretion of phosphoric acid follows a fall in the white blood-corpuscle curve, pointing to an increased destruction of white corpuscles, there is associated with this increase a corresponding increase in the amount of uric acid excreted. In thirteen instances there is confirmatory evidence of increased destruction

of the white cells obtained from the differential counts, whilst in three instances this confirmation, owing to the absence of differential counts, could not be obtained. In five instances the examination of the differential counts gave a directly opposite interpretation to the study of the white corpuscle and phosphoric acid curves, the one pointing to increased destruction, the other not. Most of the observations were on cases of advanced pulmonary tuberculosis; in these we may fairly assume, as Haig (11) has pointed out, that there is no retention of uric acid within the body.

If we carefully examine the curves we shall see that in those cases in which there are great and sudden variations in the number of white cells there are also great and sudden variations in the amounts of uric acid and phosphoric acid excreted. This tends to confirm the theory that uric acid is derived from the white corpuscles (compare, for instance, Nos. 1 and 5 on the one hand with the earlier observations on Nos. 10 and 11 on the other). We also observe that in the case of the three children (Nos. 1, 2, and 3) there is, relatively to the body-weight, more uric acid and phosphoric acid excreted than in the case of the adults. We may explain this by assuming a more rapid destruction of the white cells in the former case than in the latter. This is confirmed by reference to the curves, when we find that the rise of uric acid and phosphoric acid follows more closely on the fall of the white corpuscle curve than in the case of the adults.

As regards methods: the white blood-corpuscle counts were made by the Thoma-Zeiss hæmacytometer, the diluting solution used being a $\frac{1}{3}$ per cent. solution of acetic acid in water coloured by gentian violet; the differential counts were made from films fixed by heat and stained by a modification of Ehrlich's triacid stain. The uric acid was estimated by Hopkins' method (by Folin's modification in the case of J. L—): 100 c.c. urine were used for each estimation, and the total quantity passed in twenty-four hours being measured, the total quantity of uric acid passed in twenty-four hours was thus calculated. The phosphoric acid was estimated by means of the volumetric method with uranium nitrate, 50 c.c. urine being used for each estimation, and the total quantity passed in the



It is to be noted, in regard to this and the succeeding charts, that the heights above the base line of the different points on the three curves give respectively the weights in grammes of uric acid and phosphoric acid excreted in twenty-four hours, and the number of white blood-cells per cubic mm., on the dates shown above the columns.

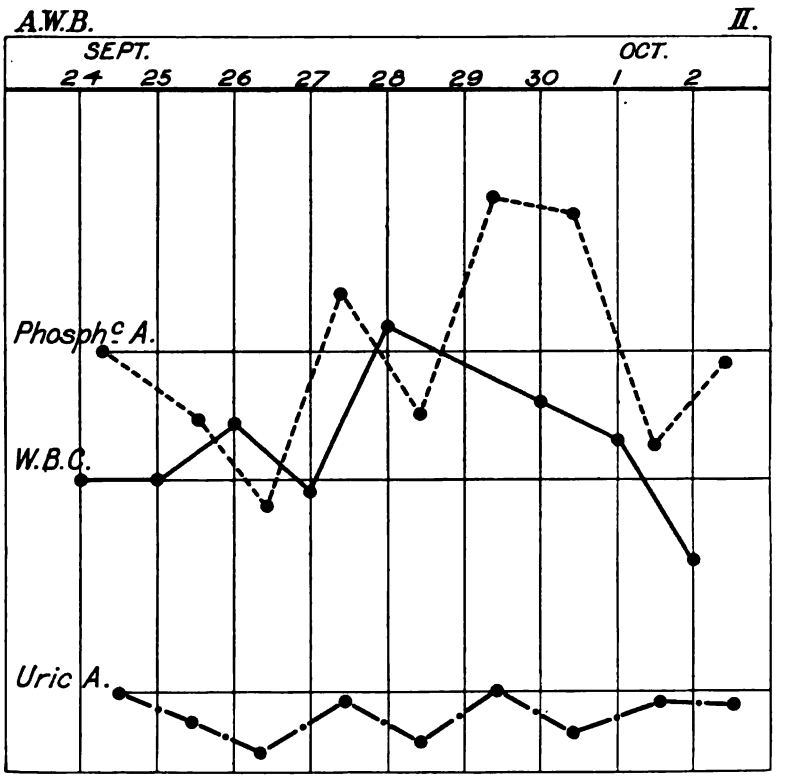
twenty-four hours being calculated as in the case of the uric acid.

I append tables and curves of the results obtained in the different cases. The observations were made on eleven patients, and the results include upwards of a hundred estimations of uric acid. The numbers in the columns headed uric acid and phosphoric acid are the amounts (in grammes) of these substances respectively passed in the urine in twenty-four hours. The columns headed w. b. c. show the number of white blood-corpuscles per cubic millimetre. The columns under the headings "young cells" give the percentage of cells having the characters intermediate between those of myelocytes and polymorphonuclear neutrophiles as described above. Owing to unavoidable accidents the continuity of the observations was unfortunately broken in places, and in the short description of the results which I shall now give only those differential counts will be discussed which have a definite bearing on the subject of this paper.

Case 1.—E. T—, male, aged 10 years. Weight 3 st. 13 lbs. Lymphadenoma with intermittent temperature. On examining the curves and tables we see that there are two rises in the phosphoric acid curve corresponding with two rises in the uric acid curve following falls in the white corpuscle curve, also one rise in the phosphoric acid and uric acid curves corresponding with a fall in the white corpuscle curve. From a study of the differential counts we find evidence of breaking down (increased destruction) of the white cells between March 15th and 16th, 22nd and 23rd, and finally April 16th and 17th, such evidence being, as I stated above, a decrease in the absolute number of polymorphonuclear neutrophiles; whilst the number of the myelocytes and young cells remains the same or even increases. These three occasions correspond with the three above-mentioned falls in the white corpuscle curve.

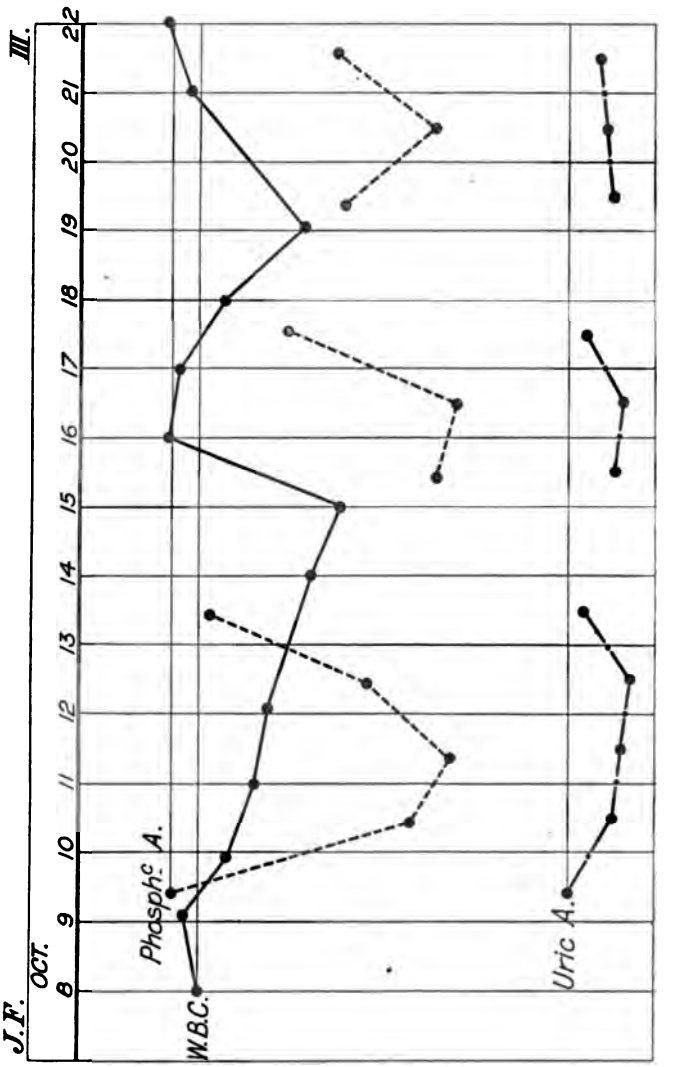
Case 2.—A. W. B—, male, aged 7 years. Weight 2 st. 10 lbs. Chronic pulmonary tuberculosis; pyuria. There are seen to be marked rises of the phosphoric acid and uric acid curves (on September 27th and 29th) respectively following

falls in the white corpuscle curve. Following the last fall in the white corpuscle curve is a rise in the phosphoric acid curve, but not in the uric acid curve. From the differential counts there is evidence of breaking down of the white corpuscles between September 26th and 27th, also between September 30th and October 1st, or in two out of the three instances in which a study of the three curves points to increased destruction of the white cells. Between September 28th and 29th no differential counts were made.



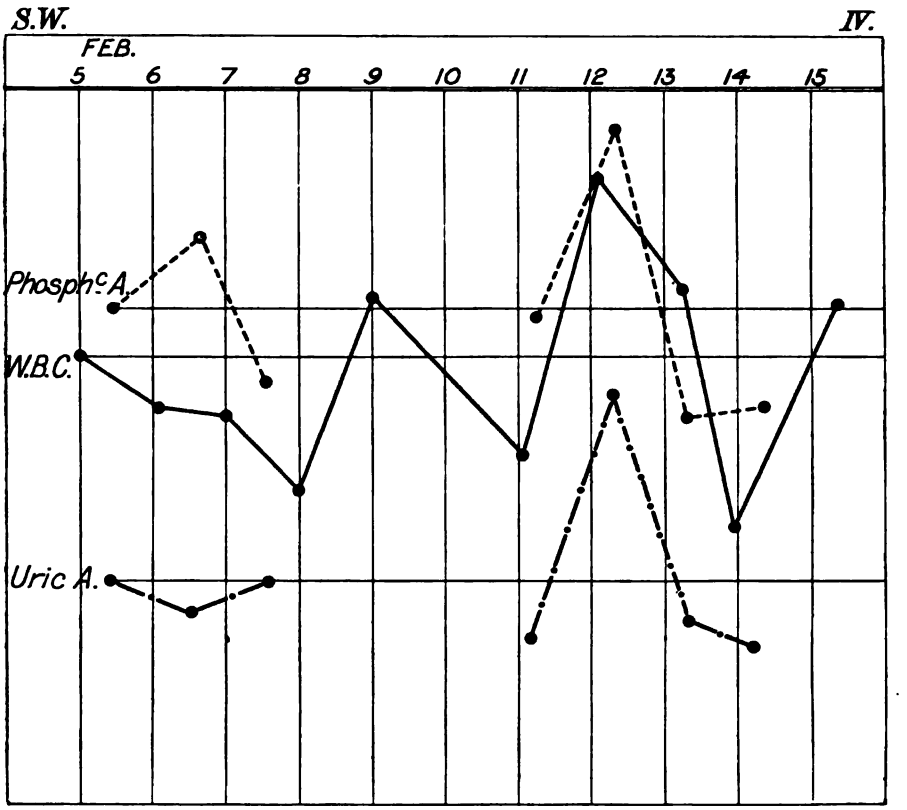
CASE 3.—J. F—, male, aged 7 years. Weight 3 st. Chronic pulmonary tuberculosis. Here we find two rises in the phosphoric acid and uric acid curves immediately following falls in the white corpuscle curve. From an examination of the differential counts there is evidence of increased destruction between October 11th and 12th corresponding to one of these two falls. Between October 16th and 17th, corresponding to

the other white corpuscle fall, there is no evidence of increased destruction from the differential counts, except perhaps in regard to the small lymphocytes.

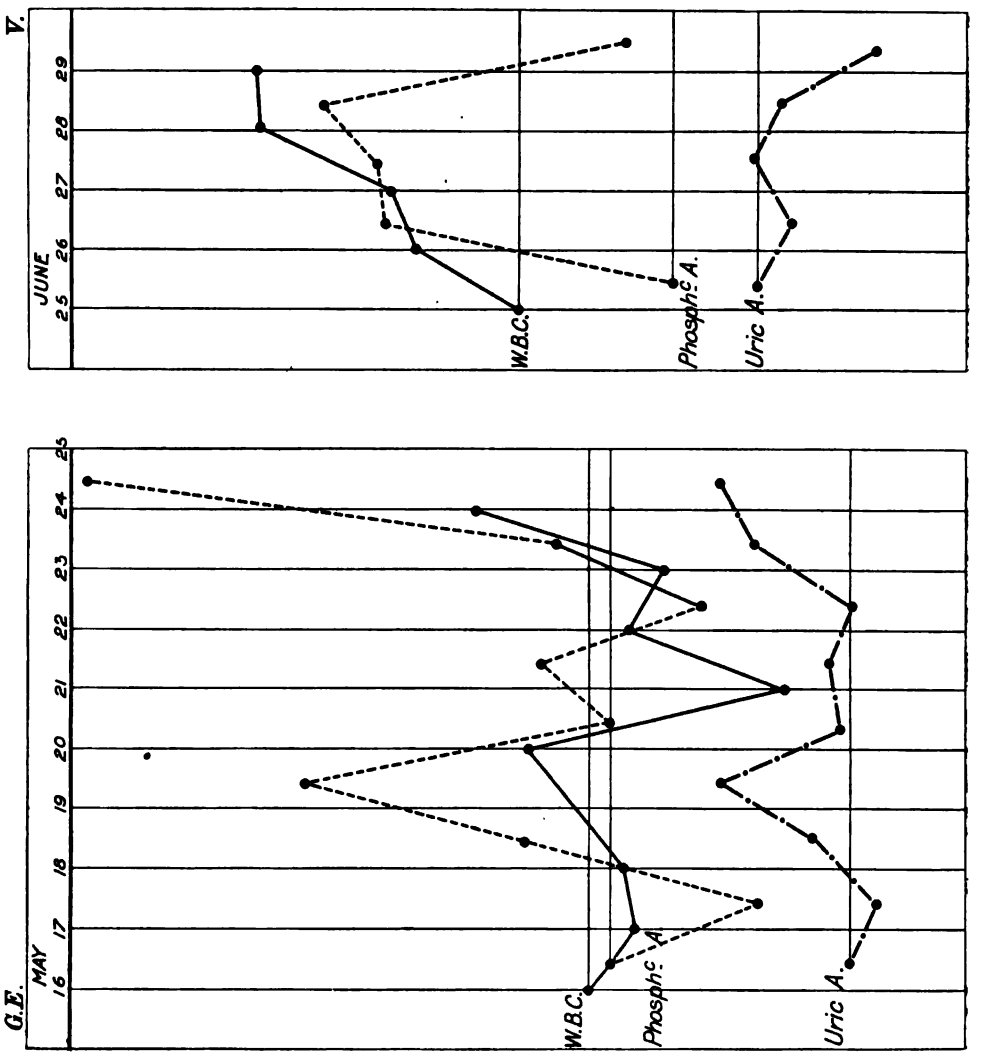


CASE 4.—S. W—, male, aged 20 years. Caseous pulmonary tuberculosis. Patient died on February 16th. In this case we find marked rises in the phosphoric acid and uric acid curves

following one fall in the white corpuscle curve (between February 9th and 11th). Unfortunately no differential counts were made between February 9th and 11th.

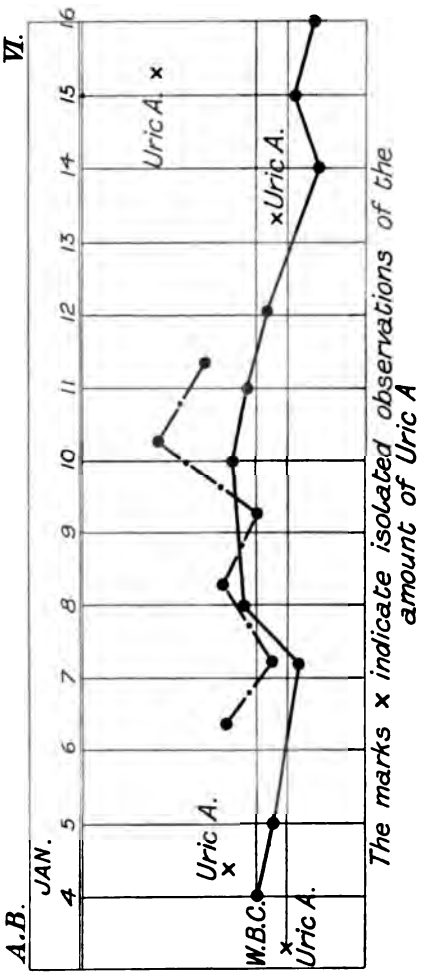


Case 5.—G. E—, male, aged 21 years. Caseous pulmonary tuberculosis. This patient died on June 30th. On examining the tables and curves we see two well-marked rises in the phosphoric acid and uric acid curves following falls in the white corpuscle curve, also a slight rise of each following a fall in the white corpuscle curve. In only one instance is confirmatory evidence of increased destruction to be obtained from the differential counts, viz. between May 16th and 17th. Between May 20th and 21st and May 22nd and 23rd there is no confirmatory evidence of increased destruction.



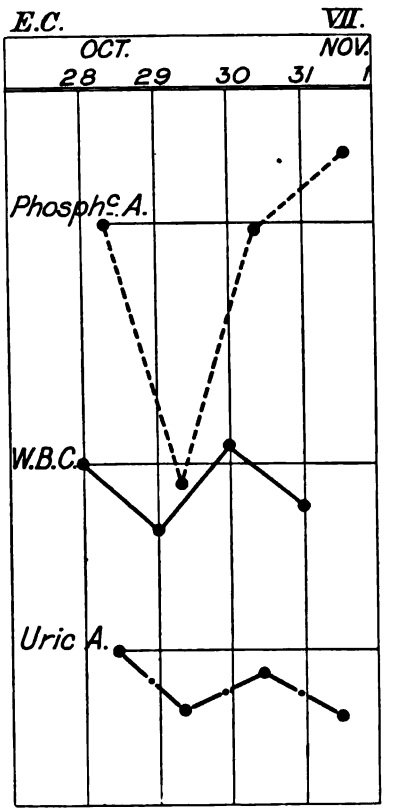
CASE 6.—A. B—, female, aged 21 years. Caseous and miliary pulmonary tuberculosis. Unfortunately no estimations of phosphoric acid and no continuous differential counts were made in this case. It may be noted, however, that after each fall in the white corpuscle curve there is a rise in the uric acid curve, the most marked rise (that between January 13th and 15th) occur-

ring after the longest and most marked fall in the blood-corpuscle curve. The low white corpuscle counts in this case should be noted.



CASE 7.—E. C—, female, aged 36 years. Caseous and miliary pulmonary tuberculosis. Here we see that after the fall in the white blood-count between October 28th and 29th there are marked rises in the curves of phosphoric acid and uric acid. No confirmatory evidence of increased destruction is obtain-

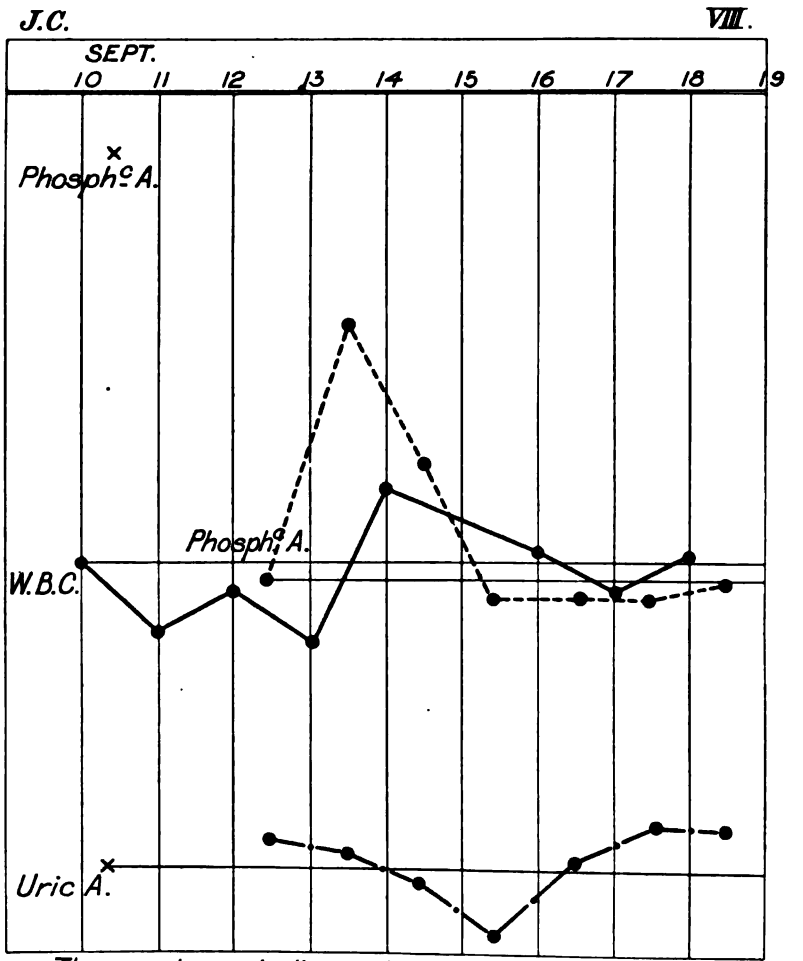
able from the differential counts between October 28th and 29th.



CASE 8.—T. C—, male, aged 21 years. Caseous pulmonary tuberculosis.

Here there is nothing in confirmation of the theory that uric acid is produced by the destruction of the white blood-corpuscles. There are two rises in the phosphoric acid curve following falls in the blood-corpuscle curve between September 10th and 11th and September 16th and 17th respectively, but neither of them corresponds with a rise in the uric acid curve. From the differential counts we find that there is evidence of increased destruction of the white cells between September 10th and 11th, 12th and 13th, and finally 16th and 17th. The first and last of these three occasions correspond,

then, to the two periods of increased destruction as shown by the white corpuscle and phosphoric acid curves. In the second case, however, there is no succeeding rise in the phosphoric acid curve, and therefore no other evidence of increased destruction.

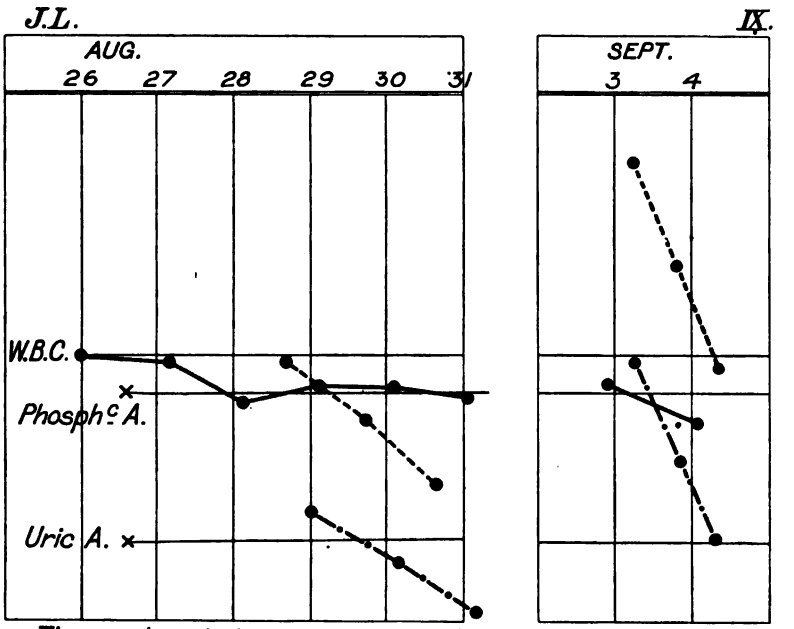


The marks x indicate isolated observations of the amounts of Phosphoric A. and Uric A.

CASE 9.—J. L—, male, aged 40 years. Chronic pulmonary tuberculosis.

In this case it is probable that a rise in the phosphoric acid and uric acid curves occurred soon after the 31st inst., following

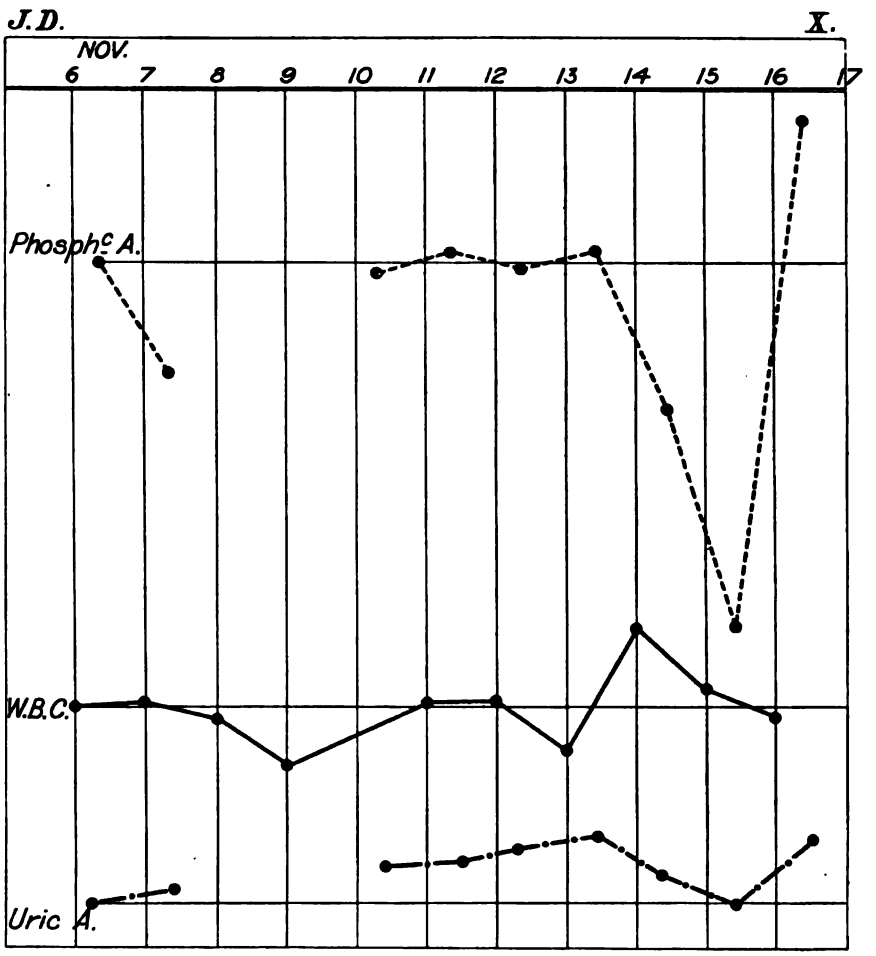
a slight fall in the white corpuscle curve. There is evidence of increased destruction from the differential counts between August 29th and 30th. Here there is little evidence either for or against the theory.



The marks × indicate isolated observations of the amounts of Phosphoric A. and Uric A.

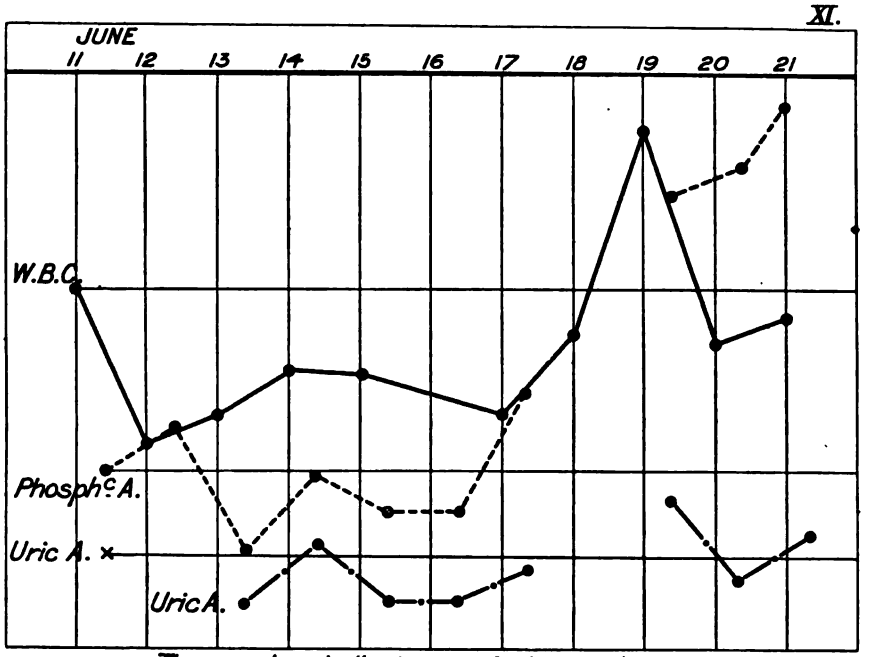
Case 10.—J. D—, male, aged 62 years. Chronic pulmonary tuberculosis; bronchitis; emphysema.

Here we see two rises in the phosphoric acid and uric acid curves, slight ones on November 13th, very marked ones on November 16th, following two falls in the white corpuscle curve. From a study of the differential counts we obtain confirmatory evidence of increased destruction of the white corpuscles between November 12th and 13th, corresponding to the first of these occasions. Corresponding to the second there is no confirmatory evidence, seeing that no differential count was made either on November 14th or 15th.



CASE 11.—E. H—, female, æt. 42 years. Probably new growth of mediastinum. Patient died on June 22nd. In this case there are three corresponding rises in the phosphoric acid and uric acid curves, following respectively three falls in the white blood-corpuscle curve. There is corresponding to these three occasions confirmatory evidence of increased destruction of the white blood-corpuscles between June 11th and 12th, 14th and 15th, and finally between June 19th and 20th.

XI.



The mark × indicates an isolated observation of the amount of Uric acid.

Date.	P_2O_5 in grms.	Uric acid in grms.	W. B. C.	Differential counts. Polymorphonuclear neutrophiles.	Lymphocytes. Large.	Lymphocytes. Small.	"Young cells."	Myelocytes.	Eosinophiles.
March	No. 1.—E. T—.			Per ct.	Per ct.	Per ct.	Per ct.	Per ct.	Per ct.
13	--	—	22280	—	—	—	—	—	—
14	·42	·18	17250	75·18	14·07	4·20	3·75	1·49	1·29
15	·25	·21	13200	72·72	18·19	3·86	3·40	·71	1·10
16	·94	·36	11800	71·38	19·02	3·10	4·37	·54	1·55
17	·62	·33	—	—	—	—	—	—	—
18	·52	·21	12900	78·46	14·73	3·15	2·43	·14	1·05
19	·76	·30	13500	74·82	13·54	5·19	4·20	·75	1·48
20	1·47	·40	—	—	—	—	—	—	—
21	·62	·21	21330	79·38	5·63	6·76	6·44	·48	1·28
22	·32	·08	14500	74·47	14·01	7·53	2·71	·62	·62
23	1·01	·47	13950	68·89	10·84	13·07	5·90	·31	·95
24	·47	·15	—	—	—	—	—	—	—
25	·85	·22	18640	65·91	13·81	16·78	3·14	·17	·175
26	—	·21	12150	75·65	8·05	13·85	·93	0	1·49
27	—	·094	13600	66·08	12·65	14·93	3·86	0	2·46
28			11930	—	—	—	—	—	—
April									
16	·59	·19	6260	71·23	7·79	16·63	0	0	4·33
17	·80	·25	5630	71·38	5·20	14·14	5·04	0	4·22
18	1·02	·29	—	—	—	—	—	—	—

Date.	P_2O_5 in grms.	Uric acid in grms.	W.B.C.	Differential counts. Polymorphonuclear neutrophiles.	Lymphocytes. Large.	Lymphocytes. Small.	"Young cells."	Myelocytes.	Eosinophiles.
No. 2.—A. W. B—.									
Sept.				Per ct.	Per ct.	Per ct.	Per ct.	Per ct.	Per ct.
24	1·37	·30	9690	56·24	10·26	27·48	1·42	0	4·58
25	1·18	·17	9700	62·43	7·85	24·00	1·71	0	4·00
26	·89	·088	11560	55·54	12·39	25·65	2·33	·14	3·93
27	1·56	·24	9200	53·38	4·77	34·00	1·69	2·30	3·84
28	1·18	·12	14600	66·24	10·58	19·89	·91	0	2·37
29	1·90	·28	—	—	—	—	—	—	—
30	1·85	·13	12200	57·34	7·48	30·36	1·55	0	3·25
Oct.									
1	1·08	·23	11000	60·70	7·44	26·78	1·74	0	3·33
2	1·35	·22	7100	54·59	7·08	31·56	1·28	·48	4·99
No. 3.—J. F—.									
Oct.									
8	—	—	16460	—	—	—	—	—	—
9	1·70	·30	16830	49·92	8·37	37·96	1·94	0	1·79
10	·87	·15	15150	51·67	8·29	38·11	·63	0	1·27
11	·75	·12	14400	53·34	8·47	35·36	1·33	0	1·48
12	1·01	·094	14000	45·78	8·44	43·18	2·04	0	·54
13	1·57	·25	—	—	—	—	—	—	—
14	—	—	12430	60·73	3·23	33·67	·44	0	1·91
15	·79	·13	11250	50·60	9·07	37·90	2·01	0	·40
16	·72	·11	17400	55·73	5·57	35·98	1·43	0	1·27
17	1·29	·25	17000	67·44	2·54	27·25	·69	0	2·07
18	—	—	15130	61·82	9·23	27·83	0	0	1·11
19	1·06	·15	12530	57·14	6·10	33·92	1·78	0	1·04
20	·81	·17	—	—	—	—	—	—	—
21	1·13	·20	16700	60·00	6·40	30·62	2·03	0	·93
22			17500	60·19	6·47	30·42	1·13	·16	1·61
No. 4.—S. W—.									
Feb.									
5	1·70	·77	15200	79·75	4·63	8·96	6·02	·15	·46
6	1·93	·67	13600	85·78	4·47	7·18	2·07	0	·48
7	1·44	·76	13400	77·21	5·84	10·54	5·41	·99	0
8	—	—	10850	80·91	4·56	10·64	3·54	·17	·17
9	—	—	17380	75·48	2·45	12·25	9·10	·17	52
10	—	—	—	—	—	—	—	—	—
11	1·70	·65	12050	—	—	—	—	—	—
12	2·30	1·42	21500	85·52	4·25	8·51	1·53	·17	0
13	1·34	·67	17500	84·21	5·08	8·42	1·93	·35	0
14	1·38	·56	9600	87·46	4·12	5·44	2·80	·16	0
15			17000	86·05	3·26	7·78	2·71	·18	0

Date.	P_2O_5 in grms.	Uric acid in grms.	W. B. C.	Differential counts. Polymorphonuclear neutrophiles.	Lymphocytes. Large.	Lymphocytes. Small.	"Young cells."	Myelocytes.	Eosinophiles.
	No. 5.—G. E—.			Per ct.	Per ct.	Per ct.	Per ct.	Per ct.	Per ct.
May 16	1·49	·49	15700	83·93	6·15	3·96	4·16	1·38	·40
17	·89	·38	13580	79·51	6·20	7·51	5·07	·75	·94
18	1·82	·62	14100	80·07	5·71	6·23	6·75	·17	·69[1]
19	2·74	1·04	—	—	—	—	—	—	—
20	1·49	·54	18300	81·44	5·30	8·90	2·08	·57	1·51[2]
21	1·77	·59	7900	85·74	3·61	6·22	2·61	·20	1·60
22	1·08	·49	14000	78·92	5·23	8·24	6·02	·31	1·27
23	1·69	·89	12570	81·61	6·35	9·62	1·20	·17	1·03
24	3·62	1·05	20270	80·25	6·87	4·93	5·99	1·23	·70
25	—	—	—	—	—	—	—	—	—
June 25	1·22	·85	18500	90·71	3·48	2·65	1·16	1·99	0
26	2·40	·74	22800	85·55	1 82	2·82	6·64	3·15	0
27	2·44	·87	23800	87·07	1·30	3·60	4·41	3·60	0
28	2·66	·77	29250	88·87	4·17	2·26	2·60	2·08	0
29	1·42	·34	29500	—	—	—	—	—	—
	No. 6.—A. B—.								
Jan. 4	—	·29	3600	—	—	—	—	—	—
5	—	·47	3166	—	—	—	—	—	—
6	—	—	—	—	—	—	—	—	—
7	—	·49	2400	—	—	—	—	—	—
8	—	·33	4300	—	—	—	—	—	—
9	—	·49	—	—	—	—	—	—	—
10	—	·37	4600	—	—	—	—	—	—
11	—	·71	4111	—	—	—	—	—	—
12	—	·55	3400	—	—	—	—	—	—
13	—	—	—	—	—	—	—	—	—
14	—	·30	1600	—	—	—	—	—	—
15	—	—	2500	—	—	—	—	—	—
16	—	·70	1750	—	—	—	—	—	—
	No. 7.—E. C—.								
Oct. 28	1·97	·53	11700	70·54	6·84	19·42	1·75	0	1·43
29	1·11	·31	9300	73·28	4·92	19·70	·59	0	1·49
30	1·93	·44	12100	60·86	4·46	29·58	4·16	·15	·77
31	2·18	·30	10130	68·30	8·92	17·26	2·52	·59	2·38
	No. 8.—T. C—.								
Sept. 10	2·65	·28	12830	81·11	3·22	10·44	3·99	·76	·46
11	—	—	10600	76·43	6·56	10·77	4·37	·67	1·17
12	1·22	·37	11900	80·95	5·39	8·73	2·38	·16	2·38
13	2·09	·35	10300	80·20	3·49	6·84	7·42	·43	1·60
14	1·62	·24	15500	82·82	4·42	8·33	1·87	·17	2·38
15	1·18	07	—	—	—	—	—	—	—
16	1·18	·30	13400	83·12	5·34	5·62	3·89	·14	1·87
17	1·17	·43	12000	81·95	3·41	7·31	3·90	·32	3·08
18	1·24	·41	13150	84·87	3·81	8·81	·39	—	2·10
19			—	—	—	—	—	—	—

[1] Also basophiles, ·35 per cent. [2] Also basophiles, ·19 per cent.

Date.	P_2O_5 in grms.	Uric acid in grms.	W.B.C.	Differential counts. Polymorphonuclear neutrophiles.	Lymphocytes. Large.	Lymphocytes. Small.	"Young cells."	Myelocytes.	Eosinophiles.
Aug.	No. 9.—J. L—.			Per ct.	Per ct.	Per ct.	Per ct.	Per ct.	Per ct.
26	·75	·27	8750	62·55	5·92	28·12	2·01	0	1·38
27	—	—	8550	63·82	8·68	24·89	·57	0	2·02
28	·86	·35	7400	64·99	3·34	25·41	2·73	·30	3·19
29	·69	·22	7830	67·00	7·96	21·41	1·73	·14	1·73
30	·46	·064	7600	63·94	3·91	27·55	2·89	0	1·70
31	—	—	7150	61·72	6·43	28·21	1·32	·49	1·81
Sept.									
3	1·51	·86	7750	57·83	8·02	27·13	4·45	·13	2·42
4	·83	·25	6500	64·73	5·64	25·23	2·19	0	2·19
5									

Date.	P_2O_5 in grms.	Uric acid in grms.	W.B.C.	Differential counts. Polymorphonuclear neutrophiles.	Lymphocytes. Large.	Lymphocytes. Small.	"Young cells."	Myelocytes.	Eosinophiles.	Basophiles.
Nov.	No. 10.—J. D—.			Per ct.	P. ct.	P. ct.	Per ct.	Per ct.	Per ct.	Per ct.
6	2·43	·17	8700	65·74	6·06	22·95	1·80	·16	2·78	·49
7	2·03	·21	8830	54·96	6·23	28·89	5·38	0	3·96	·56
8	—	—	8150	—	—	—	—	—	—	—
9	—	—	6550	63·91	5·15	25·15	2·06	·21	3·29	·21
10	2·41	·29	—	—	—	—	—	—	—	—
11	2·48	·30	8700	66·61	5·07	22·76	2·15	0	2·77	·61
12	2·42	·35	8820	64·64	4·70	24·73	2·73	0	2·88	·30
13	2·50	·39	7020	62·37	5·30	26·67	2·47	0	2·82	·35
14	1·94	·24	11450	—	—	—	—	—	—	—
15	1·12	·15	9050	—	—	—	—	—	—	—
16	2·94	·36	8360	66·36	3·69	24·58	2·40	0	2·58	·36
17			—	—	—	—	—	—	—	—

Date.	P_2O_5 in grms.	Uric acid in grms.	W.B.C.	Differential counts. Polymorphonuclear neutrophiles.	Lymphocytes. Large.	Lymphocytes. Small.	"Young cells."	Myelocytes.	Eosinophiles.
June	No. 11.—E. H—.			Per ct.	Per ct.	Per ct.	Per ct.	Per ct.	Per ct.
11	·64	·27	12700	51·97	11·21	31·43	·79	·15	4·42
12	·79	—	7300	58·81	7·05	30·79	1·48	0	1·85
13	·34	·17	8300	54·24	5·59	34·06	1·35	0	4·74
14	·63	·38	9900	55·89	11·77	26·36	2·81	0	3·15
15	·49	·17	9760	52·04	16·83	23·97	2·89	·17	4·08
16	(mean of 2 days) ·49	·17	—	—	—	—	—	—	—
17	(mean of 2 days) ·93	·29	8160	64·24	4·23	24·40	1·69	·338	5·08
18	—	—	11050	67·35	5·33	25·27	·15	0	1·88
19	1·59	·54	18300	68·11	12·07	14·97	3·22	·16	1·45
20	1·70	·24	10700	70·33	12·12	11·80	3·82	1·27	·48
21	2·11	·39	11600	69·32	10·41	15·719	2·65	1·13	·76
22			—	—	—	—	—	—	—

To Dr. Eustace Smith, and to my colleagues at Victoria Park Chest Hospital, Drs. Heron, Beale, Sainsbury, Glover Lyon, and Sir Hugh Beevor, I am indebted for permission to use the results obtained from cases under their care.

REFERENCES.

1. *Horbaczewski* (*J.*).—"Untersuchungen über die Entstehung der Harnsäure im Säugethierorganismus," 'Wien. Sitz.-Ber.,' Bd. xcviii, Abth. iii, S. 301; also 'Sitzungsb. d. k. Akad. d. Wissensch. Math.-Naturw. Cl.,' Wien, 1889, xcviii, 301—318; also 'Sitzungsb. d. k. Akad. d. Wissensch.,' 1890, Bd. xlviii, 1891; Bd. c, 1892. Also "Beiträge zur Kenntniss der Bildung von Harnsäure und der Xanthinbasen, sowie der Entstehung der Leucocyten im Säugethierorganismus," 'Monatssch. f. Chemie,' xii, 221—275; and cf. J. Horbaczewski 'Zur Theorie der Harnsäurebildung im Säugethierorganismus,' Wiesbaden, J. F. Bergmann, 1892.
2. *Kühnau* (*W.*).—'Zeit. f. klin. Med.,' 1895, vol. xxviii, p. 534, "Experimentelle und klinische Untersuchungen über das Verhaltniss der Harnsäureausscheidung zu der Leukocytose;" also Kühnau (W.) und F. Weiss, "Weitere Mittheilungen zur Kenntniss der Harnsäureausscheidung bei Leukocytose und Hypoleukocytose, sowie zur Pathologie der Leukämie," 'Ztsch. f. klin. Med.,' Berl., 1897, xxxii, 482—500.
3. *Richter* (*P. F.*).—"Ueber Harnsäureausscheidung und Leukocytose," 'Ztschr. f. klin. Med.,' Berl., 1895, xxvii, 291—311.
4. *Douglas* (*Carstairs C.*).—"Some Observations on the Excretion of Uric Acid, with Special Reference to its Connection with Leucocytosis," 'Edinb. Med. and Surg. Journ.,' 1900, N. S., vii, 32—42.
5. *Zarnier* (*G.*).—"Rapporto tra leucocytosi ed eliminazione di acido urico," 'Gazz. d. Osp.,' Milano, 1896, xvii, 676–9.
6. *Giagmis* (*C.*).—"La genesi dell' acido urico in rapporto alle sostanze nucleiniche," 'Gazz. d. Osp.,' Milano, 1898, xix, 545–7.
7. *Reale* (*E.*).—"Il ricambio della nucleina in rapporta alla genesi dell' acido urico ed alla patologia delle affezioni uricemiche," 'Clin. mod.,' Pisa, 1898, iv, 169–71, 185, 225.
8. "The Metabolism of the Nucleins under Physiological and Pathological Conditions," by T. H. Milroy, M.D., B.Sc., Assistant to the Professor of Physiology, Edinburgh University, and J. Malcolm, M.B., 'Journal of Physiology,' Supplement, 1898-9; also 1899-1900.
9. *W. Hale White and F. Gowland Hopkins.*—'Journal of Physiology,' 1899, "On the Excretion of Phosphorus and Nitrogen in Leukæmia."
10. *Cabot.*—'Clinical Examination of the Blood.'
11. *Haig.*—'Uric Acid as a Factor in the Causation of Disease.'
12. *Ehrlich and Lazarus.*—'Histology of the Blood,' translated by W. Myers, chap. ii.

March 3rd, 1903.

32. *A case of "acute leukæmia," with a scheme of classification of leukæmias and pseudo-leukæmias.*

By F. Parkes Weber.

A very anæmic man, Wilhelm R—, a native of Germany, aged 49 years, was admitted into the German Hospital for purpura, etc., on September 13th, 1902, and died on the following day. I did not see the man myself during life, but notes were taken by the house physician, Dr. Quosig. According to the patient's wife his illness commenced about eight weeks before his death. The gums were swollen and bled easily, and he had spots on the skin. He suffered from pain in the throat, headache, and pains in the back, and lost flesh. Previously to the final illness he seems generally to have enjoyed good health. There was no history of syphilis or alcoholism. His wife, who looked healthy, had had eight children (four were still living, four dead) and four miscarriages. About twelve months ago he had some abdominal discomfort and pain. He once had influenza, and had often suffered from his throat, but paid little attention to it.

Condition on day of admission (September 13th, 1902).—The patient was very anæmic, and there were dark violet-red cutaneous petechiæ over the whole body. Temp. 100° F. Pulse about 114 in the minute. Dyspnœa. There was a kind of muttering delirium, but he could answer questions. The breath had an offensive smell. The gums were pale and swollen, the tonsils were enlarged so as almost to touch each other, and the uvula was œdematous. The tongue was moist and somewhat coated. On the left cheek there was a dark reddish circumscribed swelling about the size of a small chestnut, which was discharging a thin purulent material from an opening in its centre. According to the patient this lump had been present eight days. The cervical, axillary, and inguinal lymphatic glands were moderately enlarged. Slight bronchitic sounds were heard over the lungs, and a systolic murmur was audible over the apex of the heart. The spleen was enlarged, and the lower edge could be felt three finger-breadths below the ribs.

The liver was perhaps enlarged. No ascites. Œdema about the ankles. Knee-jerks active. Slight ankle-clonus. Plantar reflexes natural. Sensation natural. Pupils equal, react to light. Urine: sp. gr. 1012, acid, some albumen, no sugar.

Next morning the patient's temperature was 100·4° F. In spite of strychnine and subcutaneous transfusion of normal salt solution the weakness steadily increased, and death occurred about 5 p.m.

The Blood.

The blood was unfortunately not examined during life. That present in the heart at the *post-mortem* examination had a peculiar brownish-pink appearance, as if it were mixed with milk, and films were taken for microscopical examination. There was no poikilocytosis, and the erythrocytes were well preserved, as was well seen on examining blood in sections of the tissues. The white cells were immensely increased in number, in some parts occupying nearly as much of the field as the red cells, yet after examination of the blood in blood-vessels seen in the microscopic sections of the organs I think that the relative proportion of white cells to red cells would have been found to be much less had the blood been examined during the patient's life. Dr. G. L. Eastes kindly made the following differential count of the white cells for me:—Small lymphocytes 36·4 per cent., large lymphocytes 56·3 per cent. (total lymphocytes 92·7 per cent.), polymorphonuclears 0·2 per cent., eosinophiles 1·1 per cent., myelocytes 2·4 per cent., eosinophile myelocytes 3·6 per cent. This count represents the composite result arrived at by counting a fairly large blood film in five different parts, 200 white cells being enumerated in each part. The size of the lymphocytes appeared to depend upon the thickness with which the blood was spread. Dr. Eastes thought that the lymphocytes were in general of medium size, tending rather to the large than the small form. The percentages of the other cells present varied in different parts of the same film. He found about one erythroblast per 100 white cells.

Necropsy.

The heart weighed fourteen ounces. There was no pericardial effusion, but there was a localised patch of pericarditis over the

middle of the front of the heart,[1] and many petechiæ under the visceral layer of the pericardium. The cardiac muscle was exceedingly pale and flabby. There was no valvular disease.

The *lungs* were somewhat œdematous. There was a little scarring at both apices, and old pleuritic adhesion over part of the right lung.

The *spleen* was enlarged, weighing twenty-six ounces, and was of a soft "chocolate pudding" consistence and colour.

The *liver* was enlarged and very pale. It weighed ninety-six ounces. Microscopic examination accounted for some of the increase in weight of the organ, for the interlobular spaces were found packed with leucocyte-like cells, the distribution of the change resembling that of the interlobular cell-infiltration in commencing hepatic cirrhosis. I shall later on return to the microscopic examination.

The *kidneys* were pale, and weighed sixteen ounces together. The capsules stripped readily. A minute whitish patch in the cortex of one kidney was examined microscopically, and showed an accumulation of leucocyte-like cells similar to those in the interlobular spaces of the liver. I shall later on describe the microscopic characters of these cells.

The *pancreas* macroscopically showed nothing noteworthy.

The *stomach* showed petechial submucous hæmorrhages. In the intestines nothing abnormal was seen, but they were very incompletely examined.

All the mesenteric *lymphatic glands* were considerably enlarged. One of them from near the hilum of the liver was selected for microscopic examination (see later).

The *brain* (weight fifty-one ounces) showed nothing abnormal except that the pia mater seemed to be infiltrated with blood.

Of the enlarged superficial lymphatic glands of the body the supra-condylar gland from one elbow was removed for microscopic examination (see later).

Bones.—One femur and one humerus were examined. The cancellous tissue in the head of each of these bones contained pale marrow, but the marrow in the shafts was chiefly of a creamy brownish-red colour, sometimes seen in the contents of a

[1] This patch apparently corresponded to the "milk-spot" often seen on the front of the heart, and confirms the view that such "milk-spots" may sometimes be due to a former patch of pericarditis ("epicarditis").

liver abscess, but not diffluent. A piece of this marrow from the shaft of the humerus was removed for microscopical examination (see later). The sternum and ribs contained reddish marrow. A shoulder-joint and a hip-joint were examined and appeared normal.

Microscopic examination.

Sections were made (1) of the bone marrow from the shaft of the humerus; (2) of a piece of the spleen; (3) of two lymphatic glands; (4) of a piece of the liver; and (5) of a piece of a kidney. The methods of staining employed were—(*a*) hæmatoxylin or hæmatoxylin and eosin; (*b*) Ehrlich's triacid mixture; (*c*) Mann's long method by the biacid mixture of methyl blue and eosin.[1]

(1) *The bone marrow from the shaft of the humerus.*—The space normally occupied by fat-vesicles is much encroached on by blood and leucocyte-like cells. The whole tissue may be said to be permeated[2] with these colourless cells, almost all of which can be divided into two kinds:

(A) Mononuclear cells without distinct granules, of about the diameter of a red blood-corpuscle on the average and evidently of the same nature as the lymphocyte-like cells in the man's blood, though many of them have rather more protoplasm around the nucleus. Almost all these cells are mononuclear, but the nucleus is often not spherical; sometimes it is indented on one side, sometimes it is lobed, and sometimes there are two or three nuclei in the same cell.

(B) Granular mononuclear cells, apparently of the myelocyte class. By Mann's eosin-methyl-blue method the granules of these cells are more or less coloured by the eosin, and many of the cells can be termed coarsely granular eosinophile. They are, on the average, slightly bigger than the preceding class of

[1] *Vide* G. Mann, 'Physiological Histology,' 1902, p. 216.

[2] I have avoided saying that the tissues are "*infiltrated*" with the cells, because the word "infiltrated" implies that the cells have been deposited in the tissues from the blood, a conclusion which I think is not yet justified in regard to cases like the present one. For the same reason I have in this paper altogether avoided speaking of leukæmic or lymphocytic "*infiltration*" or "*deposit*." The word "*permeated*" was kindly suggested to me by Dr. A. E. Garrod as a way out of the difficulty.

cells (A), and have relatively more protoplasm. The nucleus, which has frequently an eccentric position on one side of the cell, is not always round. It is sometimes elongated, and sometimes appears to be undergoing division, and sometimes there are two nuclei in the same cell.

In most parts the non-granular cells (Class A) are more numerous than the granular cells (Class B), but in some parts the two classes of cells appear equally numerous.

(2) *The spleen.*—The splenic tissue is permeated with cells of the two classes described as A and B in the preceding description of the bone marrow; it is doubtless in great part to this that the organ owes its increase in size and weight. I will not describe these cells again. In many parts the granular cells (B) are as numerous as the non-granular lymphocyte-like cells (A), and in some parts even more numerous; but in most parts the non-granular cells (A) are more numerous, and the cells in the Malpighian corpuscles belong almost entirely to the non-granular class.

(3) *The lymphatic glands.*—Amongst the non-granular lymphocyte-like cells there is throughout a good admixture of granular cells similar to those described as Class B in the account of the bone-marrow; in some parts of the sections the granular cells are very numerous.

(4) *The liver.*—I have already described the change in this organ, and have only to add that the leucocyte-like cells, which have chiefly accumulated between the lobules (interlobular distribution), but likewise to a lesser extent between the columns of hepatic cells (intercellular distribution), are partly of the non-granular lymphocyte-like class (A), and partly of the granular class (B). The former (A) are decidedly the most numerous, though in some parts of the sections there is a good proportion of the latter (B).

(5) *The kidney.*—In some parts of the patch permeated with leucocyte-like cells[1] already referred to, the lymphocyte-like cells (Class A) predominate, but in other parts the granular cells (Class B) seem to be as numerous or even more numerous.

I must thank Mr. S. G. Shattock and Dr. J. H. Drysdale for kindly looking over the microscopic specimens with me, and

[1] I do not use the term leukæmic "infiltration" or leukæmic "deposit" for the reason given in a former foot-note.

Professor R. Muir, of Glasgow, for kindly examining sections of the bone-marrow, spleen, and liver. I was particularly anxious to have Professor Muir's opinion about the granular cells in the affected tissues. He writes, "I have examined the sections you sent me, and I have no doubt that the cells in question are eosinophiles. Some of them, especially in the spleen and marrow—in fact, a large proportion of them in these two sites,—have the characters of eosinophile myelocytes. I have never seen eosinophile cells in such numbers in the tissues in lymphatic leukæmia, yet the case appears to be of that nature."

Remarks.

A good many cases of "acute leukæmia" have been published, and I must refer to the papers by W. Ebstein,[1] by A. Fraenkel,[2] by J. Rose Bradford and H. Batty Shaw,[3] by A. G. Phear,[4] etc., for an account of the subject. I shall only consider some of the numerous questions which arise.

The stomatitis, tonsillitis, and signs of microbic infection in acute leukæmia cases of this class have been supposed to separate them pathologically as well as clinically from the more chronic cases. This deduction is, however, scarcely justified as yet. An unhealthy condition of the gums and mouth may occur in many conditions other than acute leukæmia,—for instance, in chronic leukæmia, in splenic anæmia (including Banti's disease), in Hanot's disease, etc. It is quite possible, therefore, that the stomatitis and microbic infection may not be the cause of the blood-change with which they are associated in cases of acute leukæmia. There is no satisfactory clinical evidence that acute leukæmia is infectious, for Obrastzow's[5] apparent instance of infection is not sufficient.

[1] "Ueber die acute Leukämie und Pseudoleukämie," 'Deut. Arch. für klin. Medicin,' 1889, vol. xliv, p. 343.

[2] "Ueber acute Leukämie," 'Deut. med. Wochenschrift,' 1895, Nos. 39—45.

[3] "Five Cases of Acute Leukæmia," 'Medico-Chirurgical Trans.,' London, 1898, vol. lxxxi, p. 343.

[4] "A Case of Acute Leukæmia," 'Medico-Chirurgical Trans.,' London, 1901, vol. lxxxiv, p. 453.

[5] "Zwei Fälle von acuter Leukämie," 'Deut. med. Wochenschrift,' 1890, No. 50, p. 1150. A young man aged 17 years, in the Alexandra Hospital at Kiev, died of acute leukæmia about four weeks after the first symptoms of the disease. He had gangrenous ulceration of the soft palate, and abundant

In the present case the clinical history is typical, but, as in most cases, there is no absolute evidence to show when the changes in the blood first commenced.

In all or nearly all cases of acute leukæmia the blood-changes seem to have been those of lymphatic leukæmia, the increase in the colourless corpuscles of the blood being mainly due to the great number of cells of the large and small lymphocyte types. Obrastzow's two cases,[1] like a few others, were possibly exceptions, for he says that the white blood-cells in both cases were chiefly mononuclear and "faintly granular."

The present case is remarkable amongst cases of acute leukæmia on account of the great number of myelocyte-like cells present in the blood-forming tissues, yet the greater proportion of colourless cells both in the blood and in the tissues belonged to the lymphocyte type. The term *acute lymphatic leukæmia* is therefore justified for this case, as for most other cases of "acute leukæmia." Yet it is probable that cases of "acute leukæmia," such as the present one and Obrastzow's two cases,[2] ought to be regarded as representing a primitive and *relatively undifferentiated form of leukæmia* (see later on), characterised by extremely rapid progress and by all the leucocyte-forming tissues being involved at once. It is, however, also possible that, as in many cases of "acute leukæmia" there has been evidence of microbic infection as well as of leukæmia, the presence of granular cells in the blood and tissues may represent a reaction to such infection, complicating the signs of lymphatic leukæmia. On the whole, "acute leukæmia" is probably a more primitive or less differentiated type of disease than the more chronic forms of lymphatic leukæmia; but doubtless "intermediate cases" occur, and there is no hard and fast line to be drawn. Typical "spleno-medullary leukæmia" is probably the most "highly differentiated" form of leukæmia.

The question arises, whence are the lymphocyte-like cells in

micrococci were found *post mortem* in one of the lymphatic glands. Forty-one days after this patient's death a rather thin and pale man aged 32, who had attended on him in the hospital, fell ill himself with acute leukæmia, and developed a kind of hæmorrhagic stomatitis. He died fourteen days after the commencement of the symptoms.

[1] Loc. cit. See also remarks in the addendum at the end of my paper.

[2] Loc. cit.

the blood of cases of lymphatic leukæmia derived? Excluding possible multiplication in the blood-stream itself, are they found solely in the lymphatic glandular tissues of the body (spleen and lymphatic follicles and glands), as some have maintained,[1] or are they formed also in the bone-marrow? Their abundance in the bone-marrow in many cases has suggested the view that the bone-marrow is one of the sites of their production, and that it is not merely infiltrated from the blood-stream by cells produced in the lymphatic glands and spleen. But the recent observations of A. Dennig[2] and C. H. Melland[3] seem to settle this question conclusively. They have each of them published a case of acute lymphatic leukæmia (lympho-cythæmia) in which *post mortem* practically no change was discovered in the leucocyte-forming tissues other than the bone-marrow, thus proving that not only may the lymphocyte-like cells in the blood be partly derived from the bone-marrow, but even that in some cases of the disease the bone-marrow may be the almost exclusive site of their production.

This point leads me to the subject of the origin of the other forms of white corpuscles seen in leukæmic blood, and the nature of the different forms of leukæmia.

Granting that in healthy persons the lymphocytes are exclusively formed in the lymphatic glandular tissues of the body, and that the neutrophile myelocytes are the parents of the polymorphonuclear leucocytes of the blood, and are only found in the bone-marrow, it does not follow that the same rule is maintained in cases of leukæmia. If we admit that a non-granular cell of the large lymphocyte type, normally seen in the germinating centres of lymphatic glands, is the predecessor in the lymphatic glandular tissues of the ordinary lymphocytes, and in the bone-marrow of the granular myelocytes (and thus indirectly of the polymorphonuclear leucocytes of the blood),[4] the following "tumour-formation" theory of the various kinds

[1] Prof. R. Muir (Allbutt's 'System of Medicine,' vol. v, p. 642), speaking of the bone-marrow in lymphatic leukæmia, says, "The condition is really a lymphocytic infiltration of the bone-marrow, this tissue being secondarily affected in the same way as other organs."

[2] 'Muenchener med. Woch.,' January 22nd, 1901, No. 4, p. 140.

[3] 'Medical Chronicle,' September, 1902, p. 372.

[4] *Vide* the various writings of A. Pappenheim and other authors on the subject.

of leukæmia appears the most probable, or at least the most plausible.

(1) All forms of leukæmia are to be regarded as due to a *hyperplasia-like tumour-formation* in the leucocyte-producing tissues of the body, the tumour-cells (which more or less resemble true leucocytes) overflowing or being attracted out into the blood-stream. (2) If in this tumour-formation the less differentiated (more primitive) cells, viz. the non-granular cells of the large lymphocyte type, either those of the lymphatic glandular tissues or those of the bone-marrow, or those of both, be the cells chiefly involved (that is, if they are to be regarded as the "parents of the tumour-cells"), the result will be a condition of lymphatic leukæmia (lympho-cythæmia), and in the most acute cases the blood will generally contain more cells of the large lymphocyte type than cells of the small lymphocyte type. (3) If, on the other hand, the more differentiated cells, viz. the granular cells of the bone-marrow, be the cells chiefly involved in the tumour-formation, the result will be a condition of myelogenic or spleno-medullary leukæmia, and the tumour-cells in the tissues and blood will resemble myelocytes and ordinary polymorphonuclear leucocytes. (4) "Spleno-medullary" leukæmia, according to this theory, is to be regarded as a higher and more differentiated type of disease than lymphatic leukæmia (that is, it is to be regarded as due to a tumour-formation of a less embryonic type), and this supposition agrees with the fact that in its development and course it is generally less rapid. (5) In some cases of leukæmia, especially spleno-medullary leukæmia, it is possible that cells of the large lymphocyte type in the lymphatic glands and spleen may become granular like similar cells in the bone-marrow normally do. That is to say, it is possible that the myelocyte-like cells found in the spleen and lymphatic glands in such cases have not merely been deposited there from the blood-stream, but may have developed *in situ* from cells of the primitive large lymphocyte type. (6) According to this theory any leukæmia differs from any leucocytosis (including lymphocytosis) in that the former is due to an inroad of tumour-cells from a hyperplasia-like tumour-formation in the leucocyte-producing tissues of the body, whilst the latter is merely the expression of a tissue reaction which may occur in health as well as in disease. A leucocytosis is therefore, strictly speak-

ing, never an early stage of leukæmia; yet a true leucocytosis may perhaps be followed by true leukæmia, in so far as a reactive growth in the leucocyte-producing tissues (of which reactive growth the leucocytosis is the expression) may be supposed to give a start to a tumour-formation (of which the leukæmia is the expression), just as chronic irritation of the skin sometimes acts as the exciting cause of epithelioma.

If we carry this theory a little further all primary hyperplasia-like tumour-formations in the leucocyte-producing tissues of the body may be regarded either as leukæmias or as pseudo-leukæmias (using the German terms for convenience), and the question arises, why do the newly formed cells escape (overflow or become attracted) into the blood-stream in cases of leukæmia, and not in cases of pseudo-leukæmia? In the pseudo-leukæmias the tumour cells, though more or less closely resembling leucocytes, and originally derived from the leucocyte-forming tissues of the body, may have become so modified in the process of tumour-formation that, unlike the leucocyte-like cells of leukæmia, they may have lost the power of entering (being squeezed into or attracted into) the blood-stream, or have lost the power of persisting in a living state in the circulating blood. I do not think, however, that the main difference between a leukæmia and a pseudo-leukæmia can be explained merely on the mechanical theory that when the bone-marrow is the site of a rapid growth the contents of the medullary cavity are likely to be partly forced out into the blood-stream, owing to the fact that they are confined by walls which, unlike the capsules of the spleen and lymphatic glands, are rigid and scarcely distensible.[1] In some cases of multiple myeloma all the ribs have been crammed full and even bulged out with growth, and yet there has been no escape of cells into the circulating blood sufficient in amount to notably increase the proportion of colourless corpuscles.

It seems to me that the whole class of leukæmias and pseudo-leukæmias may be divided into the following six types, independently of intermediate forms:

(A) A new growth of lymphocyte-like cells originating in the bone-marrow and not overflowing into the circulating blood. Myelogenic pseudo-leukæmia (using leukæmia in the sense of

[1] See A. Pappenheim, 'Virchow's Archiv,' 1901, vol. clxvi, p. 473.

lympho-cythæmia), myelogenic lympho-sarcoma, lymphadenomatosis of bones, multiple myeloma (myelomatosis) of the lymphatic type.

(B) Similar to the preceding, but the lymphocyte-like cells enter or are drawn into the blood-stream. Myelogenic lymphocythæmia (viz. some cases of acute lymphatic leukæmia).

(C) A new growth formed in large part of lymphocyte-like cells originating in the lymph-glands, or lymphadenoid tissues generally, and not to any great extent overflowing into the circulating blood. Lymphatic or splenic lymphadenoma or pseudo-leukæmia (using leukæmia in the sense of lymphocythæmia), Hodgkin's disease. In the more chronic and fibrous varieties of this type the microscopic appearances differ of course considerably from those in acute cases.

(D) Similar to the preceding, but the lymphocyte-like cells invade the blood-stream. Lymphatic or splenic lympho-cythæmia.

(E) A new growth of cells derived from the myelocytes of the bone-marrow and not invading the circulating blood. Myelogenic pseudo-leukæmia (using leukæmia in the sense of myelogenic or spleno-medullary leucocythæmia). To cases of this type or partaking of this type the term multiple myeloma (myelomatosis) might perhaps be limited.

(F) A new growth characterised by its myelocyte-like cells overflowing into the circulating blood. Bence-Jones albumosuria never occurs in this type, though it sometimes does in the preceding type (E). *May 19th*, 1903.

[An addendum will be found at the end of the volume.]

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33. *Congenital cystic disease of the liver in an infant.*

By Leonard S. Dudgeon.

In April, 1903, a boy aged 9 months, was admitted to the East London Hospital for Children, under the care of Dr. Coutts, with the following history:

He had wasted for the last ten weeks. There had been no vomiting, but a slight attack of diarrhœa during this period. There had been no rash and no discoloration of the skin. The

child had been breast-fed until a few days before admission to the hospital, when the diet was altered for cow's milk and barley-water. It is not known for certain whether the child had ever been given alcohol. There had never been any previous illness. The parents were healthy, and six other children were healthy.

On admission.—The child was very anæmic and wasted. Temperature was subnormal, 95° F. Thrush was present on the roof of the mouth and dorsum of tongue. Abdomen was not distended. The edge of the liver was felt about two fingers' breadth below the costal margin. There was no ascites. Spleen was not enlarged. Nothing else abnormal was found in the abdomen. The child was very rickety. There was nothing abnormal noted in the chest.

A few days after admission, the signs of broncho-pneumonia developed at both bases. The temperature during the height of the broncho-pneumonia, and during the whole of the "stay" in the hospital, varied between 85° and 98° F. Death took place nine days after admission. There was never any jaundice; not even the slightest discoloration of the skin or conjunctiva was noticed, and the stools were always bile-stained.

The *post-mortem* examination was performed in my absence by Dr. Branson. There was nothing abnormal noticed in the skin or appendages. There was well-marked evidence of rickets in most of the bones. The body was very much wasted. There were scattered patches of broncho-pneumonia and collapse in the lower lobes of both lungs, but the heart and pericardium were healthy.

Abdomen.—The peritoneum was normal, and there was no ascites. Spleen, kidneys, pancreas, intestines, and supra-renals were healthy.

Liver.—This organ was enlarged; the lower edge almost reached to the level of the umbilicus. The surface was smooth and the capsule was not wrinkled or thickened. The glands in the portal fissure were not enlarged. The bile-ducts were apparently normal, but no careful dissection was made along the course of the ducts. The liver substance was light yellow colour, with minute white specks scattered in all directions throughout the tissue. The organ was very tough and cut with great resistance. There were no naked-eye changes beyond those already mentioned.

Microscopical specimens were prepared and stained with hæmalum and eosin, van Gieson's stain, and with the various amyloid reagents. The most characteristic feature of each microscopical specimen are the large patches of fibrous tissue, which have both a unilobular and multilobular distribution. In the fibrous tissue we find elongated spindle-cells and leucocytes, and both large and small spaces lined with columnar epithelium.[1] These spaces are of variable size, but there are many which are very long and tubular, and in every case the lumen is quite clear. A large number of sections have been examined, but

FIG. 30.

Showing the presence of tubular spaces in the connective tissue between the lobules.

only a few show the typical worm-shaped groups of cells which we see arranged in the fibrous patches in cases of biliary cirrhosis, and which have been considered to be new-formed bile-ducts. In many of the specimens, however, one can see groups of small cell spaces identical with those met with in biliary cirrhosis. There do not appear to be any cell groups which could be described as "the reverted cells of Adami." The walls of the bile-ducts are normal, and also the blood-vessels. The liver cells do not show any microscopical changes except for a few vacuoles which are present in some of the cells. Sections

[1] It has been found that coloured fluids injected into the bile-ducts do not pass into the cystic spaces found in cystic disease of the liver.

were stained with methyl violet, etc., but with negative results. Personally, I thought I was dealing with an example of biliary cirrhosis, but Dr. Rolleston, who very kindly examined some of the sections for me, considered that the specimen was an example of congenital cystic disease of the liver.

LITERATURE.

The literature on this subject is very scarce; except for papers by Still, Rolleston, and Kanthack, there is little to be found.

Still (1), in vol. xlix of these 'Transactions,' refers to a most interesting case of a child, aged 7 weeks, brought to the Great Ormond Street Hospital with the following history:—Wasting had been noticed from birth (eight months child). There had been enlargement of the abdomen since the child was fourteen days old.

On admission.—Fairly healthy-looking child, good colour, no jaundice. The liver was not noticed to be abnormal, and there was no ascites. A mass was felt in each flank, vaguely uniform in outline. The urine contained a large quantity of albumen, and micturition was more frequent than normal. Death occurred nine days after admission, with convulsive movements which were probably uræmic in origin.

At the *post-mortem* examination the infant was found to weigh 6½ lbs. The kidneys were very large (15 oz.). The capsule stripped easily, but the surface presented a translucent appearance due to the large numbers of closely packed cysts, situated more especially in the cortex. The liver appeared to be of normal size. The surface showed some greyish branching lines which suggested some excess of fibrous tissue beneath the capsule. There were no cysts visible to the naked eye, except on the cut surfaces lying in the fibrous trabeculæ. Gall-bladder and the main ducts were normal. All other parts of the body were normal.

Microscopical examination.—There was dilatation of the tubes throughout the kidneys, and excess of the fibrous stroma. In the liver there were two well-marked changes: (1) a great excess of fibrous tissue; (2) a large number of irregular branching cavities lined with cubical or subcubical epithelium. There was an excess of connective tissue, and it was found to have an

irregular distribution. The liver cells did not show any degeneration or vacuolation.

Still (1) also quotes a case which had been under the care of Dr. Rolleston, of a stillborn infant which was found to have congenital cystic liver and kidneys. The kidneys were cystic throughout, while the liver was very similar to Still's own case. The child also had webbed toes, six fingers on one hand, and an occipital meningocele.

A very full account was given by Rolleston (2) and Kanthack in Virchow's 'Archives' of a similar case to the above in an infant four weeks old. It is rather a matter of surprise that although many cases of congenital cystic kidneys have been published in adults, there is little to be found on the disease in children.

Still compares the disease in infants and adults, and remarks on the similar condition in the two cases, except that the tubules are more dilated and the kidneys larger in many cases in adults.

Mr. Shattock (3) considers that the cystic condition of the kidneys is the result of a congenital malformation, the mesonephros having blended with the metanephros in the development of the kidney. It seems, therefore, that the infantile and the adult cases are examples of the same cause, but that the latter is sometimes in a more advanced stage. Still also states that the microscopical appearances in the two cases are similar, except that the spaces are more dilated in the adult form.

Various causes have been given to account for these changes:

1. Cirrhosis, similar to that supposed to occur in the kidney, causing dilatation of the bile-ducts and formation of new bile-ducts.

2. Vacuolation of the liver cells, possibly owing to some degenerative process within them.

3. Spontaneous proliferation of the walls of the bile-ducts, occurring in adult life, and giving rise to cavernous biliary angioma.

4. New growths (Still).

The author of the paper from which I have so freely quoted considers that the cystic liver associated with the cystic kidneys in adults, as in infants, is due to a congenital condition. He bases his theory on Mr. Shattock's observations (1) on the origin of the changes met with in congenital cystic kidneys, and con-

siders that the changes in the liver are due to a malformation, and not the result of disease. According to this theory, the cysts are derived from columns of hypoblastic cells forming part of the original duodenal diverticulum, and not from the bile-ducts. The excess of connective tissue may be explained as due to a persistence of fœtal mesoblastic tissue, *i. e.* a malformation, not inflammatory. The most interesting point in my case is that the kidneys were normal to the naked eye, but as I did not obtain any of the organs for microscopy, one cannot place much reliance on this observation. Rolleston (4) states that cystic disease of the liver is always accompanied by a similar and nearly always more advanced change in the kidneys. If this statement is really correct, we must conclude that my case is an exception to the general rule; but, as I have said before, there was no microscopical examination. Lastly, is there sufficient evidence forthcoming for the above statement? Still considers that there are two further points which help to prove his theory of the congenital origin of the cysts: (1) the presence of congenital malformations; (2) the entire absence of jaundice. There was no congenital malformation in my case, and there was never the slightest tinge of jaundice.

The relation of this condition of the liver, such as I here describe, to cystic adenoma, is one of great interest. Hoppe Seyler (5) and Quincke refer to this point as follows:—"As a sharp differentiation cannot be made, we will describe cystic adenoma and the so-called cystic degeneration as one and the same condition. Cysts hold their place among the tissue formations of the liver. Co-existing cirrhosis has frequently been observed, and some authors have even expressed this belief, that the cirrhotic process has a decided influence upon the development of the cysts."

In conclusion, my best thanks are due to Dr. Coutts for giving me permission to publish the case, and to Dr. Rolleston for his valuable opinion on the microscopical specimens which he kindly examined for me.

REFERENCES.

1. *G. F. Still.*—'Transactions of the Pathological Society of London,' vol. xlix, 1898, p. 155.

2. *H. D. Rolleston and A. A. Kanthack.*—Virchow's 'Archiv,' Bd. cxxx, pp. 488, 492.

3. *S. G. Shattock.*—'Transactions of the Pathological Society of London,' vol. xxxvii, p. 287.

4. *H. D. Rolleston.*—'Encyclopædia Medica,' vol. vi, p. 532.

5. *Hoppe Seyler and Quincke.*—Nothnagel's 'Encyclopædia of Practical Medicine,' American translation, p. 754.

May 19th, 1903.

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34. *Multiple aneurysms of the splenic artery associated with calcification and dilatation of the portal vein and its radicles.*

By R. S. Trevor.

The specimen was obtained from the body of a man aged 53, a commissionaire, who was admitted into St. George's Hospital under the care of Mr. Jaffrey in order to undergo, at his own request, a radical cure for a hydrocele, from which he had suffered for some ten years.

The patient looked ill on admission, but beyond the local trouble no definite signs could be discovered. He admitted having contracted syphilis in his youth. At the operation, which was successfully performed, it was noticed that there was a great tendency to hæmorrhage. On the following day his temperature rose to 102° F., and an examination of the chest led to the belief that a deep-seated pneumonia had developed. At the same time the liver edge was felt one inch below the costal margin, and much enlargement of the spleen was suspected, though the latter point could not be definitely decided owing to rigidity of the abdominal walls. On the second day after operation profuse diarrhœa, with hæmorrhage from the bowel, set in and persisted in spite of treatment until the man's death thirteen days later. The wound did well and healed by first intention. Towards the close the patient became noisy and maniacal, and suffered from epistaxis and bleeding from the mouth.

I performed the necropsy twenty hours after death. The body, which was somewhat emaciated, showed slight general jaundice, and the sclerotics were faintly yellow.

Two old white scars were seen on the penis at the edge of the corona glandis, and much pigmentation with scabbing was present over both shins.

On opening the thorax the right lung was seen to be firmly adherent to the chest wall. On section the upper lobe was completely fibrosed, deeply pigmented, and contained one or two calcareous nodules at the apex. The middle and lower lobes were acutely congested. The left lung showed general emphysema and was also much congested. There was general severe bronchitis.

The heart was dilated and the muscle fibrosed, this change being most marked at the apices of the papillary muscles of the left ventricular wall.

The coronary arteries were atheromatous, but their main branches at any rate were widely patent.

The arch of the aorta was dilated, but the thoracic portion of the artery was only slightly atheromatous.

On examining the abdomen, the omentum was found adherent in the right iliac fossa. It was freed and reflected upwards over the chest. A lobulated mass, giving the sense of egg-shell crackling and emitting a hollow drum-like note on percussion, was exposed to view in the region of the caudal end of the pancreas. On careful dissection it proved to be connected with the splenic vessels, which were seen to be dilated and grotesquely tortuous, the artery and vein being almost intertwined.

The splenic artery close to the hilum of the spleen was dilated into an aneurysm the size of a walnut, with thin calcified walls. This aneurysm, as is seen in the specimen, is really made up of two pouches—a smaller one the size of a small bean at the splenic end, immediately succeeded by a larger sac two or nearly three times its size. Half an inch further on the artery shows a saccular aneurysm as large as a hen's egg, with thin, completely calcareous walls. Between its origin and this aneurysm the artery is tortuous, dilated, and extensively calcified. The vein on leaving the hilum is similarly dilated and calcified, and adheres firmly to the saccular aneurysm on the artery round which it winds. At this spot it shows a fusiform aneurysmal dilatation with calcified walls, within which was found a thin layer of *ante-mortem* laminated clot. For the rest of its course the splenic vein is remarkably varicose, and the seat of extensive calcification.

The inferior mesenteric, left gastro-epiploic, and superior mesenteric veins which join it are similarly affected, the two former showing numerous calcified aneurysmal dilatations.

The portal vein was found to be much sclerosed and calcified up to its point of division, but its branches were free. It was not thrombosed.

The superior and inferior mesenteric arteries were also atheromatous, and showed calcareous plates.

The liver weighed 2 lbs. 5 oz., and was small, shrunken, and cirrhotic. On section the substance was seen to be intersected by narrow bands of fibrous tissue forming a network with a very wide mesh—a multilobular cirrhosis in the strictest sense. Microscopically the fibrous tissue was seen to be well formed, poor in cellular elements, and obviously of long standing. The cirrhotic process showed little progressive tendency.

The gall-bladder was shrunken, and contained viscid mucus.

The spleen weighed 2 lbs. 10 oz., and was much enlarged. It was surrounded by tough adhesions and showed an advanced grade of perisplenitis, the capsule being thickened and greyish white in colour. On section the splenic tissue was tough and obviously fibrosed, the vessels gaping widely and being markedly thickened. Under the microscope the meshwork of the reticulum showed a diffuse fibrosis with a relative increase of the endothelial and a diminution of the lymphoid elements.

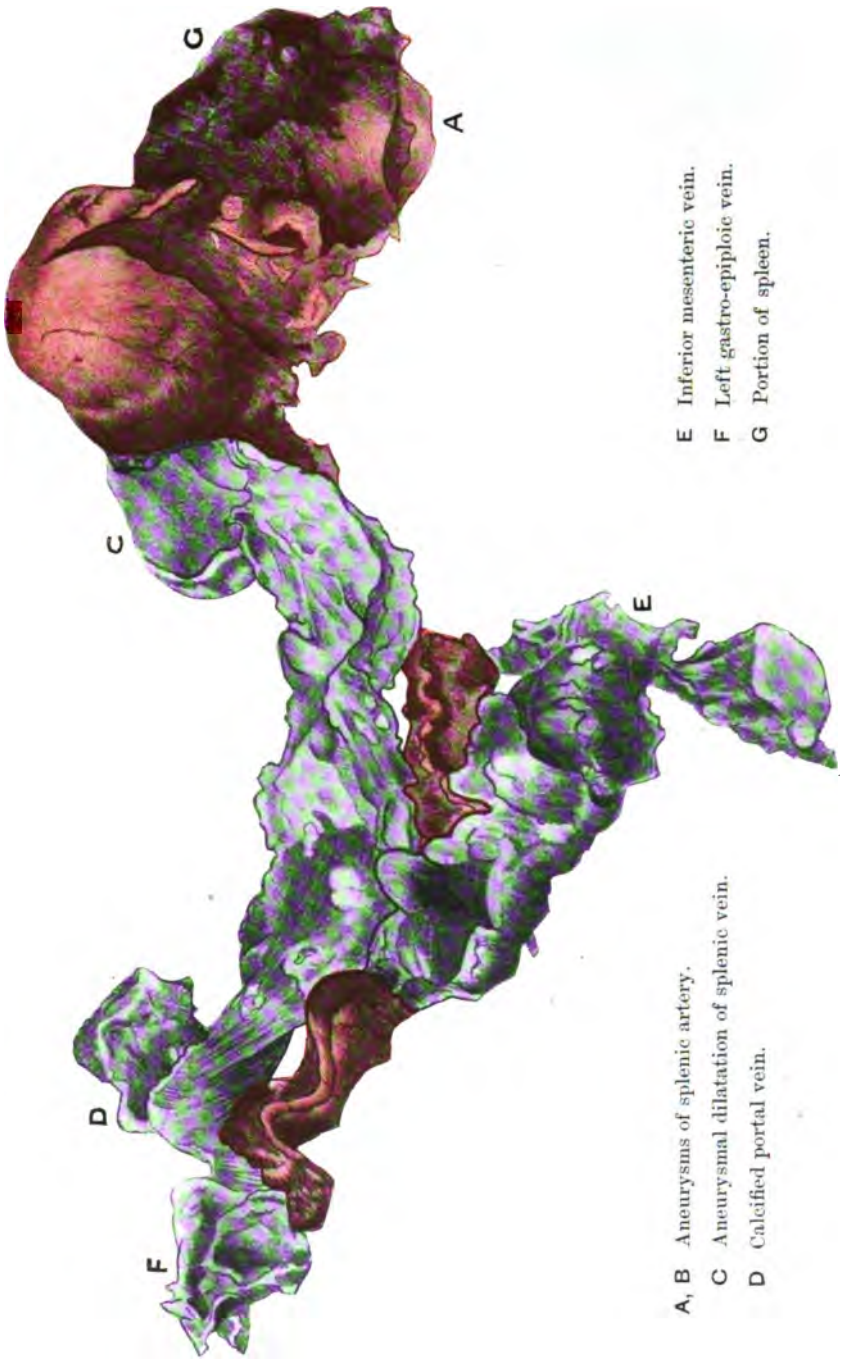
The vessels are very noticeably thickened, and here and there deposits of lime can be seen.

Neither in the liver nor the spleen could a true syphilitic endarteritis be made out. In the spleen no deposit of black pigment was noticed.

The pancreas, kidneys, and adrenals were quite healthy to the naked eye.

The alimentary canal as far as the cæcum was normal. The whole of the large gut, however, from the cæcum to the rectum was the seat of diffuse ulceration. The descending colon, sigmoid, and rectum were the most affected, the lower portion of the bowel being pigmented and ashen grey in colour. The ulcers were of the type of ulcerative colitis, irregular and sinuous in outline, undermining and destroying the mucosa, leaving here and there merely islands of the latter. There was little appearance of healing.

FIG. 31.



A, B Aneurysms of splenic artery.
C Aneurysmal dilatation of splenic vein.
D Calcified portal vein.
E Inferior mesenteric vein.
F Left gastro-epiploic vein.
G Portion of spleen.

The abdominal aorta was remarkably free from atheroma. The inferior vena cava was normal. Both testes were slightly fibrotic.

Permission to open the head was unfortunately withheld, and the brain was therefore not examined.

Aneurysm of the splenic artery is probably not so rare as might be supposed from the recorded cases, the condition being often possibly overlooked *post mortem*, as suggested by Rolleston (9), because the artery is not examined before removal of the spleen. Six cases have been recorded in this Society's 'Transactions;' only one of them, a specimen described by Lazarus-Barlow (10), showing two much smaller aneurysms affecting the same portion of the artery, at all resembles the specimen I have described. In Goodhart's (11) case there was an arterio-venous aneurysm of the splenic vessels—a valvular communication existing between artery and vein. Such a communication is not present in this case.

The changes found in the portal, gastric, splenic, and mesenteric veins must be a very rare complication or concomitant of cirrhosis. Are they to be looked upon as the result or as the cause of the hepatic cirrhosis, or is the co-existence of the two affections to be attributed to a common cause? Further, is the diseased condition of the splenic vessels and portal vein together with the cirrhosis of the liver to be looked upon as dependent upon a primary splenomegaly? In other words, have we to do with a case of Banti's disease?

Gintrac (1), Botkin (2), and others agree in thinking that chronic adhesive pylephlebitis engenders cirrhosis. Frerichs holds the opposite view. Lancereaux (4) considers that, as cases of chronic pylephlebitis leading even to obliteration of the portal vein occur, and not so rarely, without cirrhosis, and taking into consideration the numbers of cases of cirrhosis without any inflammation of the vein, together with the fact that the two conditions are found both in alcoholic and syphilitic subjects, the co-existence of the lesions is due to a common pathogenic agent affecting simultaneously the walls of the vein and the parenchyma of the liver.

Osler (5) attributes the endophlebitis of the portal vein to the heightened blood-pressure consequent upon the cirrhosis. In a case of fibroid obliteration of the portal vein of long standing he

found changes similar to those in this case in the splenic, gastric, and mesenteric veins. As a rule chronic pylephlebitis is associated with thrombosis. Whether the thrombosis is the primary lesion or a secondary result is a disputed point. The case described supports the view held by Borrmann (12) that the phlebitis is the primary lesion.

In the case I describe there was both a history and *post-mortem* evidence of syphilis. The man was a commissionaire, an old soldier, and therefore readily exposed to those insults to the system which commonly provoke cirrhosis. In addition, the soil was ready; the liver tissue devitalised by a syphilitic toxin would be all the more easily affected. The resistance of the walls of the portal vessels having been lowered in the same way, it would only remain for a heightened blood-pressure to act long enough for dilatation and calcification to follow.

There still remains, however, the question as to whether the case was not one of Banti's disease. At the outset we are met with a great difficulty, viz. the fact that no blood examination was made, and therefore the question of a definite anæmia cannot be decided. It is true that at the necropsy the body, in addition to being slightly jaundiced, was pale, but this could be accounted for by the loss of blood from the bowel. The man, however, looked ill on admission. The tendency to hæmorrhage, a point insisted on by Senator (6), the large spleen and the cirrhotic liver—the former outweighing the latter, a fact which Posselt (7) notes as characteristic,—and the man's age are all in favour of Banti's disease.

Again, the histological findings in the spleen, viz. a diffuse thickening of the reticulum and trabeculæ, and a fibrosis leading to a diminution in the Malpighian corpuscles, as well as those in the liver, viz. a wide-meshed cirrhosis formed by narrow bands of fibrous tissue, tally with those given by Banti (8). In addition, Banti speaks of plaques in the walls of the portal and splenic vein looking like atheromatous patches, due to localised endothelial proliferation; but besides this he says, "In the splenic vein are seen the lesions of a sclerotic endophlebitis, . . . and true atheromatous and calcareous patches may be found. Such changes may spread into the portal vein." It is only in the ascitic stage, however, that he has seen the mesenteric veins similarly affected.

There is, then, I think, much to be said, in spite of the want of a blood examination, in favour of the case being one of Banti's disease—a case of long, slow duration such as the disease sometimes may be—complicated, perhaps, by being implanted upon a syphilitic soil. To the influence of the latter poison may be attributed the degeneration of the coronary, splenic, mesenteric, and possibly cerebral vessels. The aneurysms of the splenic artery are but the outcome of this degeneration in the least supported area of the vessel, viz. between the tail of the pancreas and the hilum of the spleen.

The ulceration of the colon may in the same way be explained as due to a failure of nutrition, the result of the extensive vascular disease. Unfortunately, by an oversight, material from the gut was not kept for histological study.

In conclusion, I wish to express my thanks to Mr. Jaffrey for permission to publish the case, to Dr. Rolleston for the help he has given me in the preparation of this paper, and to Mr. Laurence Jones for the drawing of the specimen.

LIST OF REFERENCES.

1. Quoted by Lancereaux.
2. Quoted by Lancereaux.
3. 'Dis. of Liver,' vol. ii, p. 403, N. S. Soc. Trans.
4. 'Maladies du Foie et du Pancréas,' p. 570.
5. 'Principles and Practice of Medicine,' 4th ed., p. 773.
6. 'Berl. klin. Wochenschrift,' Bd. xxxviii, S. 1145.
7. Quoted by Senator.
8. Ziegler's 'Beiträge zur path. Anat.,' Bd. xxiv, S. 21.
9. 'Trans. Path. Soc.,' vol. l, p. 55.
10. Ibid., vol. l, p. 57.
11. Ibid., vol. xl, p. 67.
12. 'Deutsches Arch. f. klin. Med.,' Bd. lix, S. 283.

May 19th, 1903.

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35. *Cholesteatoma of the brain.*

By H. MORLEY FLETCHER.

THIS specimen was obtained from the body of a youth aged 19, who was admitted to St. Bartholomew's Hospital on September 22nd, 1902, under the care of Dr. Tooth. The

history given was that the patient fell while lifting a parcel on to a van. He was picked up unconscious and brought to the hospital. On admission he was comatose; there was no obvious paralysis, the knee-jerks were increased, and the pupils were continually dilating and contracting. The urine contained a slight haze of albumen. Later he had fits with tonic spasm. On the 23rd Cheyne-Stokes breathing set in, and on the 24th he died, the temperature just before death rising to 106°. There was a history of fits some years previously; otherwise he had always had good health.

The *post-mortem* examination was made by myself twenty-six hours after death. All the organs were healthy with the exception of the brain.

The brain weighed 48 oz; the convolutions were not flattened. There was an excess of fluid in the lateral ventricles with a slight degree of dilatation. Lying with its long axis transversely, just above the anterior corpora quadrigemina, was a tumour the size of a small walnut. The surface of the tumour was nodular, hard, and white; it possessed a lustre exactly resembling that of a pearl. It measured 30 mm. in its long axis and 26 mm. in its short axis.

The tumour lay behind the third ventricle covered over by the greatly thinned-out velum interpositum. It was difficult to say whether the tumour had arisen from the under surface of this structure or between its two layers. The choroid plexuses were natural, and the venæ Galeni were not thrombosed. At first it was thought that the tumour arose in the pineal gland, but subsequently it was found that the pineal lay close against the front of the tumour, somewhat compressed but otherwise natural. Below the tumour lay the anterior corpora quadrigemina considerably distorted by pressure. Posteriorly the lateral lobes of the cerebellum were pressed upon to a moderate degree.

On cutting into the tumour it was found to consist of a dense shell resembling fibrous tissue to the naked eye, while the central portions contained white, soft, granular material.

Microscopical sections were prepared from a segment of the tumour. These show the following features:—most externally there is a thin layer of exceedingly delicate connective tissue, next to which comes a basement membrane supporting on its

inner surface a narrow layer of epithelium of the squamous stratified variety. This layer varies somewhat in thickness, but generally consists of three to five cells. Further inwards a broad layer of apparently parallel fibres is seen, in places forming concentric laminæ. A closer examination shows, however, that these are not fibres, but are flattened cells, derived from the inner surface of the epithelial layer, closely resembling the cells of the corneous layer, of the skin. The more centrally placed cells, presumably the older ones, have undergone degenerative changes; no nucleus is visible, they stain feebly, and many show signs of swelling and disintegration. The soft matter in the centre of the tumour consists of these broken-down cells with much granular *débris* and cholesterin. No hairs or other epidermal structures have been found in the tumour.

Teased specimens from the outer dense part of the tumour show that these rows of apparently long fibres resolve themselves into large squamous cells, some with, others without nuclei, together with large numbers of cholesterin crystals.

From its appearance and structure there can be no doubt that this is a cholesteatoma, and as such one of the rarest forms of cerebral or meningeal tumours. Five cases have been recorded in the 'Transactions' of this Society since its origin—the first by Adams in 1851, another in 1854 by Peacock with a full histological account by Bristowe, two in 1859 by Hillier, and the last by Dr. Price in 1887. In these, as in the majority of cases recorded, the symptoms have generally been headache, affections of vision, occasionally epileptiform fits, and in several a sudden termination such as in the case I have described. Three of the cases reported before this Society became insane and died in asylums.

More recently Dr. Knowles and Mr. Peile have described a cholesteatoma of the floor of the fourth ventricle ('Lancet,' vol. i, 1902, p. 1833).

In nearly all the recorded cases the tumuor has been situated at the base of the brain, and I have found no instance of one occurring on the vertex or in the position of the one I have described. This distribution corresponds closely with that of the psammomata.

As to the origin of these tumours, they were first described

by Cruveilher under the name pearl-tumours, and in 1838 Müller gave them the name of cholesteatomata; but the first real investigation of their nature was by Virchow in 1854.

The best recent account is that of Glaeser,[1] in which he, in common with the majority of recent writers, regards cholesteatomata as having an endothelial origin. He describes their mode of growth as a proliferation of the endothelial cells lining the subarachnoid trabeculæ. The proliferated cells in each enclosed space become slowly compressed, thus forming a small isolated mass of cells which would represent one of the small "pearl-tumours" not infrequently found at the base of the brain. Later the trabeculæ may atrophy and the small masses become united to form a single alveolated tumour. This description applies much more closely to the psammomata than to the cholesteatomata; in the former there is evidence of an abundant proliferation of endothelial cells, while in the "pearl-tumour" such as I have described the cells are derived from a squamous stratified epithelium, and cholesterin and other products of degeneration are very conspicuous.

The question naturally arises as to what relation the pearl-tumours bear to dermoid cysts. The general structure of this cholesteatoma bears a striking resemblance to that of a dermoid cyst, and probably should be regarded as of the same nature. There is nothing to suggest an endothelial origin.

January 6th, 1903.

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36. *Primary sarcoma of the heart.*

By J. H. Drysdale.

The specimen shown is taken from a patient aged 43, who was admitted to St. Bartholomew's Hospital on March 5th, 1903.

In January of this year, being then eight months pregnant, she had a fall, and henceforward suffered from swelling of the legs and shortness of breath. On February 19th she was confined, after an easy labour, of her seventeenth child. Following the confinement the patient suffered from puerperal mania, and her general condition becoming worse, she was admitted to the hospital.

[1] 'Arch. f. path. Anat.,' 1890, Bd. cxxii, S. 389.

Previous history.—Rheumatic fever fifteen years before, and three years ago an attack of puerperal mania.

On admission.—The patient was collapsed, and her breathing frequent and laboured. There was some venous pulsation in the veins of the neck, without any marked fulness of them.

Heart.—The apex-beat was not demonstrable, and the area of cardiac dulness was not increased. The heart-sounds were feeble and irregular, but no murmur was heard. The pulse was 84, irregular, and very feeble, and the respirations 52.

The lungs natural. The liver could be felt two inches below the costal margin. There was some œdema of the legs.

The patient gradually became weaker, and died on the third day after her admission to the hospital, her pulse-rate never having reached 100, though her respirations varied between 32 and 54. For two days before her death increasing moist sounds were heard all over both lungs. The temperature on two occasions rose to 99·2°, but was otherwise subnormal.

Post-mortem examination.

Heart and pericardium.—On the anterior surface of the pericardium, externally, close to the great vessels, was an area covered with slightly raised yellowish-white masses, looking like caseating tubercles, and surrounded by a further area of considerably injected vessels.

The two layers of the pericardium were everywhere adherent. The "adhesions" between the two layers were easily broken down, and it could then be seen that the separated surfaces were covered with a rather friable, dry, almost granular material over their whole extent. At the left border of the heart there was evidence of some slight hæmorrhage having taken place, and at this spot the appearance presented was quite like that of a fibrinous exudation.

At the root of the aorta, inside the pericardial reflection, was a distinct mass of whitish new growth about the size of a small chestnut.

The parietal pericardium was everywhere infiltrated with growth, and was in places nearly a quarter of an inch thick.

After hardening, a coronal section of the heart was made from base to apex, when the following condition was disclosed:—The muscular walls of all the four chambers were infiltrated

with new growth, which for the most part had apparently penetrated from the pericardial surface, the remains of the epicardial fat being seen at some little distance from the surface in section through the left ventricle. In the walls of both auricles hardly any trace of muscle could be seen. In the posterior wall, to a great extent in the right ventricle but implicating also the septum ventriculorum, was a large rounded mass which had reached the cavity of the ventricle and destroyed the endocardium. This mass was marked externally by a boss which could be plainly seen at the back of the heart.

The aorta and pulmonary arteries were surrounded by new growth, and their outer coats to some extent infiltrated. The lumen of the aorta did not appear to be narrowed, but the pulmonary artery, and especially its left main branch, was considerably constricted.

There was some enlargement of the tracheal and bronchial glands, but only one appeared to contain any growth.

There were a few growths, the largest perhaps an inch in diameter, in the liver, and some of the lymphatic glands close to the liver were slightly enlarged and infiltrated.

Both lungs, which were much congested, were closely set with very numerous whitish growths, all about the size of a pea or rather smaller. There were no growths elsewhere in the body.

Microscopical examination shows the growth to be a sarcoma with round and oval cells of medium size, and between them a fairly well marked intercellular substance can be made out. In some of the sections of the pericardium the specimens have what looks almost like an alveolar structure, but this appearance is only owing to the nature of the tissue infiltrated, and is quite absent in the specimens from the lung, liver, and heart-wall itself. It is not possible to be quite certain where the growth originated, whether in the heart or in the pericardium; but the mass in the wall of the right ventricle and ventricular septum is quite the largest, and I think probably the primary growth. In this case it must have spread to the pericardial surface, over which it has extended, enclosing the heart as in a case, and led to infection of the parietal layer by direct contact.

The two layers of the pericardium were so easily separated that it is hardly possible to regard them as forming a continuous growth by direct extension. *May 19th*, 1903.

Report of the Section representing Morbid Anatomy, upon Dr. J. H. Drysdale's Specimen of Primary Sarcoma of the Heart.—We have examined the specimen described, together with microscopic sections of the heart and other organs, and are in agreement with the author as to the sarcomatous character of the new growth, which we also regard as having arisen in the heart. We venture to suggest that the rhythmic movements of the organ may have aided to bring about the wide local extension of the new growth.

T. W. P. LAWRENCE.
S. G. SHATTOCK.

Signed: H. MORLEY FLETCHER,
On behalf of the Members of Council representing the Section of Morbid Anatomy.

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37. *A case of membranous gastritis.*

By OTTO GRÜNBAUM.

THE diagnosis of membranous gastritis is only made during the life of the patient when shreds of tissue are vomited.

The case which came under my care ejected a complete cast of the stomach, and since I have succeeded in finding only one[1] similar case in the literature[2] on the subject I shall describe briefly the clinical aspect of the case, and then the nature of the pseudo-membrane.

The patient was a chubby girl of 3½ years, markedly rachitic. With the exception of the dyspeptic troubles, due to indiscreet diet, she had been singularly healthy. During the week preceding February 8th, 1902, she suffered from a cold. On that day, irritability suggested to the relatives that she was "sickening of some disease." Towards midnight she awoke, complained of pain in the stomach, and vomited four times during the next six hours. The following morning she seemed better and played with her dolls, but in the evening pain and vomiting returned. The tongue was thinly coated and the breath faintly foul.

[1] 'Archives of Pediatrics,' vol. xii, p. 286, J. Thomson.
[2] 'Lancet,' August, 1902.

The throat was slightly injected, but no trace of membrane visible, nor were there any diphtheria bacilli grown from a swab taken two days later. The pulse was 128, the temperature 98°. Very slight abdominal fulness was noted, but no rigidity or tenderness. Vomiting continued at short intervals. About eight in the evening on February 10th, after considerable pain and retching, a large piece of membrane was vomited, followed by a fragment eighteen hours later. The pulse persisted rapid, whilst the temperature was subnormal, and remained so throughout the illness. No epigastric tenderness could be elicited at any time. The knee-jerks were not obtainable, and did not return for five weeks. There was a transient trace of albumen in the urine. On examining the blood, 4,480,000 red cells and 8700 white cells were found, polynuclear cells 43·1 per cent., lymphocytes 48·5 per cent., hyaline 7·9 per cent., and eosinophiles 0·5 per cent. —a count which might be expected in a child of three and a half after three days' inanition.

Rectal diet had been adopted on the second day. Ox-serum, milk, starch, and chloretone constituted the nutrient enemata, a combination which was easily retained and readily absorbed; the chloretone made the child sleep for an hour or two after each injection. For ten days the stomach remained intolerant of food, and then a slow but uninterrupted recovery ensued.

The fresh membrane, on being floated out in water, was of a pinkish colour and rugous appearance. Its shape suggested that it was a cast of the stomach, the first piece which was ejected representing the cardiac opening and all except the pyloric end; the second piece completed the cast.

The microscopic examination of the pseudo-membrane showed that it was devoid of epithelial cells, and consisted of a network of fibrin, the meshes of which were filled with blood-cells. The two surfaces of the tissue presented considerable contrast, the inner being smooth whilst the outer was of distinctly ragged appearance; possibly this is due to the fact that the cast had to be partly dissolved before it could be shed. The ejection of the pyloric piece some time later than the rest lends colour to this view, since the glands at the pyloric end of the stomach do not secrete as active a proteolytic juice as those situated towards the cardiac end.

It is far from improbable that fibrinous exudations are poured

out by the mucous membrane of the stomach in various morbid conditions, but only in exceptional cases the gastric contents fail to dissolve it, and permit the formation of a pseudo-membrane. Fenwick's[1] observation that no free hydrochloric acid was present in the vomit of a child suffering from diphtheritic gastritis adds weight to this idea. The pseudo-membrane was stained and examined for micro-organisms; only a few staphylococci, mostly arranged in pairs, were found; these were not of a shape to suggest pneumococci. No bacilli were seen.

I regret that, owing to a disinfectant having been added to the vomit, cultures and inoculations were not performed.

The cause, therefore, of the disease remains unsolved. The points I would like to emphasise are:—(1) Cast of complete stomach vomited; (2) recovery of patient; (3) rapid pulse with a subnormal temperature; (4) temporary loss of knee-jerks; (5) temporary albuminuria; (6) the singular paucity of micro-organisms in the pseudo-membrane. *February 17th*, 1903.

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38. *Chronic malignant endocarditis and nephritis.*

By F. Parkes Weber.

The patient, Mrs. R. T—, aged 27 years, had albuminuria with an enlarged heart, and the signs of incompetence of the aortic valve. I do not know the early history of the case, but in December, 1901, when she was under treatment for joint pains and signs of cardiac disease, the urine was noted to be free from albumen. There was very little fever, the temperature only rarely reaching 100° F. She was an in-patient at the German Hospital from February to May, 1902, during which period her general condition varied considerably. In the latter part of April she had hæmoptysis (apparently from pulmonary embolism) and increasing dropsy. She was treated by rest in bed, digitalis, Guy's pills, and occasionally salicylate or aspirin; Southey's tubes were likewise employed for the dropsy. Up till April 10th, 1902, her temperature frequently reached 100° F. or slightly higher, but from that date to her death, on May 2nd,

[1] 'Trans. Path. Soc. of Lond.,' 1894, vol. xlv, p. 60.

1902, it remained below 100° F. The urine generally contained ¼ to ½ per mille albumen; its specific gravity when estimated was 1014 to 1020; and the daily quantity varied from about 400 c.c. to 1900 c.c. (the maximum was noted in the early part of March).

The *necropsy* was performed on the day after death. The *heart* showed much hypertrophy of the left ventricle, and weighed 24 oz. There was a patch of old pericarditis. There were numerous vegetations on the aortic and mitral valves, and on part of the endocardium of the left ventricle. Two of the sinuses of Valsalva likewise contained vegetations, and one of them (the posterior or so-called left posterior) was undergoing commencing aneurismal dilatation. Many of the vegetations were long, and, being rough and relatively hard and white, had somewhat the appearance of stalactites. They were evidently of old date. A long vegetation attached to the mitral valve was examined microscopically. It showed a fibrous tendinous structure in the interior, doubtless, as Dr. Ebbinghaus suggested to me, the remains of a chorda tendinea; the outer portion seemed to be unorganised, and had become partially calcified. For comparison, sections were likewise made of another vegetation, a small stumpy one. This seemed to consist of a central organised portion surrounded by a structureless zone, and there was a good deal of cell-infiltration at its attachment to the endocardium.

One infarct was found in each *lung*. There was moderate hydrothorax and much ascites. The *liver* was nutmeggy and weighed 94 oz. The *spleen* weighed 15 oz. and contained anæmic infarcts.

The *kidneys* weighed together 20 oz. and had something of the "large white" appearance, but were not so pale as typical "large white kidneys." In the right kidney there were two or three small contracted infarcts. Microscopic examination showed parenchymatous changes with spots of interstitial cell-infiltration.

Remarks.—The present case to some extent illustrates the connection between nephritis and what is probably a malignant form of rheumatic endocarditis.[1] This connection is, however, better shown by the following case:

[1] *Vide* "A Contribution to the Study of Malignant Endocarditis," by Dr. F. J. Poynton and Dr. A. Paine, 'Med.-Chir. Trans.,' 1902, vol. lxxxv, p. 211.

[illegible] I had under my [illegible] a woman [illegible] years with [illegible] and [illegible] There was a history of two attacks of articular rheumatism two years and [illegible] years previously. Her urine was [illegible] albumin for many months before her death, which occurred on January [illegible], 1903. The post-mortem examination showed "large white" kidneys. Microscopically a certain amount of interstitial cellular infiltration was found to accompany the parenchymatous changes. The mitral valve of the heart was practically replaced by masses of sessile vegetations, and there were similar vegetations attached to part of the endocardium of the left auricle. At the hilum of the spleen was an aneurysm of the size of a medium chestnut, doubtless of "infective" origin.

In regard to the connection between malignant endocarditis and nephritis, I would also quote the remarks of Dr. T. R. Glynn in his recent Lumleian Lectures on "Infective Endocarditis." He says:[1] "Five died with uræmic symptoms. Dr. W. Hale White has referred to uræmia as a frequent cause of death in infective endocarditis, and has described a case of this disease associated with kidney trouble where the temperature was normal for three or four weeks, the renal disease, as in several patients under my care, masking the heart affection."

I wish to draw attention to another feature of my present case (Mrs. R. T—), namely, the apparent *quiescence of the endocardial disease at a very advanced stage.* In this respect the *post-mortem* evidence (hardness of the vegetations and commencing calcification) confirmed the clinical evidence (comparative absence of fever) that in spite of the great extent of endocardial changes the endocarditis had become nearly quiescent long before the patient's death. Retrogressive or sclerotic changes in the endocardial vegetations have often been observed in persons dying from malignant endocarditis or its results, but specimens showing them to such an extent, after the disease has reached such an advanced stage as in the present instance, are probably rare. *May 19th*, 1903.

[1] 'Lancet,' 1903, vol. i, p. 1150.

39. *Bacteriological examination of a case of "acute rheumatoid arthritis."*

By G. E. Gask.

The case about to be described is that of a woman aged 29, who was admitted to St. Bartholomew's Hospital on March 25th, 1903, under the care of Dr. Tooth. I have to thank him for permission to publish the case.

History.—In January, 1903, the patient was delivered of her second child. The labour was apparently normal. Two days later the right knee-joint became red, swollen, and painful. From her history there is no evidence of sepsis. On getting up, at the end of three weeks, she found that the left knee-joint became swollen and painful. A few days later the ankle-joints became similarly affected, and she had to return to bed, where she has remained since. During the six weeks she has been in hospital the temperature has been only very slightly raised, the evening temperature never exceeding 99·6°. The appearance she now presents is that of a typical case of "acute rheumatoid arthritis," as described by Garrod, Bannatyne, and Hale White. There is marked muscular wasting. Both knee-joints are swollen and stiff; both ankle-joints and wrist-joints are similarly affected. Most of the metacarpal joints show the same changes. There is no evidence of any lipping of the bones. No lesion of the heart is discovered. The taking of salicylates has given no relief. Examination of the blood shows no leucocytosis.

Bacteriological examination.—On April 19th, 1903, 5 c.c. of fluid were drawn off from the left knee-joint. The fluid was slightly turbid and contained a fair number of pus cells and some *débris*. Film preparations made direct from the fluid showed a few cocci and one short chain of cocci, all staining badly. Cultures were made on a variety of media, but growth only occurred on a blood-agar plate. On this grew a small group of colonies of streptococci. Sub-cultures of these grew well on ordinary agar and in broth, as well as on blood agar. Some of the original fluid was incubated by itself in a sealed pipette, and after four days put into broth; a copious

growth of streptococci resulted. This streptococcus grew in rather short chains, and many diplococcic forms were present. Sub-cultures in lactose litmus broth and in litmus milk showed that it formed slight acid and that it did not coagulate milk. In these respects it resembles the ordinary *Streptococcus pyogenes*.

Animal experiments.—1 c.c. of a twenty-four-hour-old broth culture was injected subcutaneously into a mouse, and the same quantity into a rabbit, intra-venously. The mouse has remained perfectly well. The rabbit remained well till June 16th, when it was killed. *Post mortem* nothing abnormal was found.

It is not fair to draw any conclusions from this isolated case, but following on the work of others on rheumatoid arthritis it is of interest. It may be safely concluded that streptococci were present in the knee-joint. Risks of contamination from the air and from the skin were very slight, and the results were confirmed by the finding of cocci in the original films. It might be urged that this case is only one of chronic puerperal pyæmia, and this may be so. All I say is that this case appeared to be one of typical acute polyarticular rheumatoid arthritis, and that streptococci were present in the synovial fluid, and that these were apparently the cause of the disease. The suggestion is, may not other such cases be due to a similar cause? *May 5th*, 1903.

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40. *Case of basal meningitis due to streptothrix infection.*

By C. E. Beevor and E. Farquhar Buzzard.

Emma W—, aged 37, was admitted into the National Hospital for the Paralysed and Epileptic, Queen Square, on January 16th, 1903, suffering from headache and vomiting.

Family history.—No history of phthisis or consumption; one sister died of cancer of the abdomen; there was epilepsy in the father's family. Previous health good, except for epileptic fits, which she has had since ten years old, and for which she was

under the care of Dr. Outterson Wood at the West End Hospital for Nervous Diseases. Present illness was put down to hard work and worry.

Onset.—Three weeks before admission she had severe attacks of vomiting irrespective of taking food, followed next day by headache and pain in the back of the neck, both very severe and becoming unbearable, also stiffness of the neck with failing sight. One week later there was slight difficulty in swallowing, and her speech became husky.

Present condition.—On admission she had the following symptoms:—Severe pain in the back of the head, especially behind the right mastoid process, and in the back of the neck, which was held stiffly, with marked tonic contraction and tenderness of the right trapezius (superior fibres), levator anguli scapulæ, splenius, and sterno-mastoid, causing rotation of the head to the left. No definite retraction of the head. No optic neuritis. Vision $\frac{6}{9}$. Ptosis of left eyelid, and limitation of all movements of the left eye. Movements of right eye outwards defective, with coarse nystagmoid conjugate movements in all directions but especially to the right. Diplopia in looking up and down and to the left. Pupils equal and reacting to light and accommodation, but the left dilating again quickly. No paralysis of other cranial nerves. Weakness and limitation, owing to the rigid contraction of the right sterno-mastoid and trapezius, of rotation of the head to the right and of forward flexion. No wasting, no rigidity, and no paralysis of the limbs, but considerable tremor in extending the left upper limb. No anæsthesia. All the deep reflexes were well marked, with flexion of the big toe in the plantar reflex. Sphincters not affected. Irregular temperature ranging from 98·4° to 103·4°, and rising to 105° at the end.

Three days after admission she became worse and passed into a condition of stupor, with retraction of the head and arching of the spine, but this was never very severe. She had occasional twitchings of the limbs, but no fits. She became comatose, and died on January 31st, fifteen days after admission.

The diagnosis made was basal meningitis spreading down to the medulla and involving the right spinal accessory nerve, but the cause of the meningitis was not made out till the organism was discovered by Dr. Farquhar Buzzard, to whom I will leave the account of the pathological conditions.

The patient to whose clinical history Dr. Beevor has referred died on January 31st this year, and an autopsy was made four hours after death and before rigor mortis had become marked.

The vertebral column and spinal meninges appeared healthy, but in removing the spinal cord it was noticed that the cerebro-spinal fluid, especially at the base of the brain, was at high pressure and was not clear. Some of it was collected into a sterile pipette for further examination.

The bones of the cranial vault and the dura mater appeared normal, but on removing the brain a well-marked suppurative meningitis was found at the left base, extending from the optic chiasma in front to the upper end of the first cervical segment behind, and limited sharply internally by the mesial line of the pons and medulla.

As the anterior edge of the left cerebellar lobe was lifted from the inner end of the petrous portion of the temporal bone, there was an escape of pus, which led to an examination of the bone in that neighbourhood. In dissecting the periosteum off the body of the sphenoid the latter was found to be quite rotten, and this carious condition extended as far forward as the sella turcica, and backwards so as to involve the greater part of the basilar process of the occiput. The posterior clinoid processes of the sphenoid formed a sequestrum which was easily removable, but the disease had not affected the great wing of the sphenoid on either side. Both temporal bones had escaped, and there was certainly no sign of any suppuration in association with the middle ears or their neighbouring parts. The bony caries extended in the direction of the posterior nasal cavities, but its origin could not be exactly localised. The maxillary antra and their walls, and, as far as possible, the dental sockets of the upper and lower jaws, were searched, the examination throwing no light on the source of infection.

Some of the pus at the base of the brain was received into a sterile pipette and on to a sterile swab, and cover-glass smears were also made. All the internal viscera were investigated, but all proved healthy except for some hypostatic congestion of the lungs. Smears of pus taken from the base of the brain, stained by Gram, revealed the presence of an abundant streptothricial organism in the form of mycelial filaments, sometimes collected

into entangled tufts and sometimes scattered about singly or only two or three together.

In addition to these filaments were numerous short segments of varying length, which were seen either free or in short chains. The threads which went to form the tufts varied considerably in appearance when stained by Gram: some took the stain homogeneously; others took it very irregularly; a few were definitely segmented, the segments being separated from each other by short intervals in which the stain was not retained; and lastly, there were some threads which showed a chain of spherical spores towards their distal extremities. Very rarely a filament was found to end in a bulbous swelling.

Besides the elements above described, every now and then a small globular mass was found which appeared to be of fatty or gelatinous consistence, in which were embedded a large number of very short rods. On the other hand, no clubs or rosettes were to be seen. Macroscopically the pus, although thick, creamy, and of a greenish colour, contained no grains of any kind.

Better examples of the mycelial tufts were found in sections cut through small superficial abscesses which were no larger than a pea, and which were present near the surface in the substance of the cerebellum and of the temporo-sphenoidal lobe. In these the apparent branching of the filaments was a striking feature, and the constriction of the proximal end of a branch, which has been described by other observers, was occasionally noted.

With regard to its staining properties, the fungus stained well by Gram and by methylene blue, but it did not retain any colour when treated by the Ziehl-Neelsen method,—in other words, it was not acid-fast.

At my request Dr. Eastes inoculated material from the pus and cerebro-spinal fluid into broth and on to the surface of agar and blood-serum, and incubated aërobically, and into glucose-formate broth which was incubated anaërobically. All the tubes were kept under observation for nearly three weeks, but no growth occurred in any of them, so that the cultural characteristics were not obtained.

Sections of the medulla were cut and stained with logwood and eosin, and these were remarkable for the intense round-celled infiltration which occurred in and about the vessel walls, both in the pia-arachnoid and in the substance of the bulb.

Axis-cylinder processes took the logwood stain deeply and appeared to be slightly swollen. With the Nissl method most of the ganglion-cells were moderately swollen and showed commencing chromatolytic changes.[1] Sections from the medulla and from various levels of the cord stained by Busch's modification of the Marchi method showed diffuse points of degeneration scattered all through the white columns, such as are seen in various toxic processes affecting the central nervous system; the intensity of this fatty change became less marked towards the sacral end of the cord, but was still present in that region.

Smears of the cerebro-spinal fluid when stained by methylene blue showed the presence of a considerable number of partinucleate leucocytes, and of small round or oval lymphocytes, but the fluid did not contain any long filaments of mycelial growth, although what appeared to be short rods of the same character were present in very small numbers.

Our inability to grow this organism on artificial media prevents us from saying more as to its identity than that it is a member of the streptothrix group, but others, whose experience is larger than our own, may perhaps be able to narrow the number of species to which it may properly belong. It is in that hope, and on account of our conviction that the occurrence of a suppurative basal meningitis due to this form of infection is one of great rarity, that we venture to bring this case before the Society to-night. *April* 21*st*, 1903.

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41. *A case of Streptothrix infection.*

By W. D'Este Emery.

Although it has been recognised for some years that the disease known clinically as actinomycosis is not a pathological entity dependent on a single organism, yet there has been but a small number of cases recorded in which the cultural and physiological characters of the causative organism have been

[1] Corpora amylacea also present in considerable number.

fully worked out. This case is published for this reason, and not because of the rarity of the condition, or for its unusual character, for clinically it was a typical case of actinomycosis. The cultures also exhibit some points of interest, and differ in some respects from the others of which I have found records, although in some cases the descriptions have not been sufficiently full to enable one to state definitely whether the organisms were different from that present in this case.

The patient is a married woman, the wife of a farm labourer, her age being eighteen. She was admitted to King's College Hospital under Mr. Barrow (whom I have to thank for permission to publish this case) in January, 1903. Six months previously she had noticed a swelling of the left side of the face. This was attributed to a carious tooth, and the second lower bicuspid was extracted. The swelling continued to increase, and was treated by fomentations, when numerous sinuses formed over the left side of the face. Apparently no other treatment was adopted. When admitted these sinuses extended from the temporal region to the upper portion of the chest. In the right submaxillary region were two large fluctuating swellings continuous with a large tumour on the left side. In the region of the sinuses the skin and subcutaneous tissues were hard and infiltrated, and the skin uniformly red. Inside the mouth, which could only be opened half an inch, a swelling was found on the outer side of the jaw and occupying the whole thickness of the cheek. On pressure a small quantity of yellow pus could be made to exude from the site from which the second bicuspid had been extracted. The mouths of the sinuses were bounded by granulation tissue, and thin pus could be squeezed out. This pus contained very small yellowish-white granules, which felt distinctly gritty. These contained small masses of characteristic mycelium. The threads were entirely broken up into coccoid forms, no continuous threads being present. The central portions of the masses were irregularly tangled; the peripheral parts had a radial arrangement. No clubs were found.

The patient was treated with iodide of potassium, taking 60 grains *per diem*. Little improvement followed. Three weeks after admission a long incision was made below the jaw. It passed through dense fibrous tissue, which bled freely. The

sinuses were scraped and some infected skin cut away. The treatment with iodide was continued, and rapid improvement followed. The patient has been scraped a second time, and is now on the high road to recovery.[1]

Cultures were obtained from the pus of a freshly opened abscess. This was drawn up into a sterile pipette, blown into a tube of broth, and thoroughly washed. A dozen nodules were picked out and transplanted to separate tubes of agar and blood-serum, and incubated at 37° C. A single colony grew on one of the serum tubes, definite growth being apparent in five days. The following cultural and morphological characters are from primary sub-cultures from this colony. Some of the physiological characters are from more remote sub-cultures.

Solidified blood-serum.—Growth slow, the colonies attaining a size of 1 or 2 mm. in diameter in a fortnight, and then ceasing to increase in the horizontal direction, but continuing to grow vertically, forming elongated horn-like spikes projecting half a centimetre or so from the surface of the medium. When young they are opaque, white, and glistening, and are of a spherical or ovoid shape, closely resembling seed-pearls in general appearance. The medium is not liquefied or pitted.

Gelatine.—No growth at 22° C., and very little in ordinary gelatine incubated at 37° C.

Agar.—Small whitish flat colonies, never showing efflorescence. The growth appears to cease after about three weeks.

Glycerine agar.—Growth similar, but less.

Potato.—This proved to be one of the best media, growth on it being quite apparent in three or four days. The colonies are round and raised; they seldom exceed 2 mm. in diameter and 1 mm. in height, and are of a pure white colour.

Broth.—The growth forms a single lobulated mass attaining the size of a pea, or even more, in three weeks. No general turbidity, surface growth, or colonies adherent to side of tube.

Physiology.—The cultures grew almost equally well under aërobic and anaërobic conditions. In deep glucose agar stabs the upper and lower portions show almost the same amount of growth, but in surface cultures on the same media there is uniformly better growth in an atmosphere of hydrogen or

[1] She left the hospital a few days afterwards completely cured.

nitrogen than in one containing oxygen. The organism does not liquefy blood-serum or gelatine. A tube of ordinary gelatine copiously inoculated and incubated at 37° for a month showed but little growth, and the medium set completely on removal from the incubator.

The optimum temperature of growth was not determined, but the organism did not grow at 22° C. The thermal death-point was between 50° and 60° C., the cultures being exposed to the temperature for half an hour in broth.

No growth occurred in peptone-starch water. In broth to which 1 per cent. of potato starch was added growth occurred even more abundantly than in ordinary broth, and the starch slowly disappeared, but no sugar was ever found in the fluid.

No definite evidence of growth was obtained in litmus milk.

Broth cultures were inoculated intra-peritoneally and subcutaneously into two guinea-pigs. One is still alive and apparently quite healthy a month after the injection; the other was killed three weeks afterwards, and no abnormal appearances were found.

Morphology.—The characters of the pus have been described, and are in every way characteristic of those seen in streptothrical infections in general. The morphological characters of the organism as it appears in cultures vary greatly with the nature of the medium and the presence or absence of oxygen. In surface cultures on agar the organism occurs in the form of moderately thick, straight rods of very variable length, the average being about as long as a tubercle bacillus but decidedly thicker. These rods are frequently arranged in parallel groups. Clubbed forms are frequent, a single end only of the rod being enlarged. In size, shape, and general arrangement the films show a general resemblance to those of diphtheria bacilli. They stain uniformly and retain Gram's stain. No acid- or alcohol-fast forms were ever found. I am aware that it is usually held that the members of the streptothrix group do not pass through a stage in which reproduction occurs by simple tranverse fission of short rods, *i. e.* that it has a definite bacillary stage; but I have examined young and old cultures, and do not find in them any evidence in support of the view that the bacillary forms originate from the breaking down of mycelial filaments. Long forms which may be called mycelium occasionally occur, but

they are absent entirely from some specimens, and are never present in more than small proportions in comparison with the bacilli. Branching forms, if they occur at all, are extremely rare.

The organisms from aërobic cultures on blood-serum are similar, but the bacilli are much thicker and have rounded ends, resembling sausages. So characteristic is the exclusive or almost exclusive presence of bacillary forms in aërobic surface growths, that an observer investigating this case and obtaining only cultures would be almost certain to record it as "bacillary pseudo-actinomycosis," or perhaps as pseudo-tuberculosis.

Anaërobic cultures show the presence of abundant mycelium, but the filaments are in general rather short, and the lateral branches usually soon become constricted from the main stem. Young cultures stain uniformly by Gram's method, older ones show chain "spore-formation." Terminal clubbed forms are frequent, and resemble yeast-cells. These have only been found in deep stabs in glucose agar. Bacillary forms also occur in anaërobic cultures, but are relatively infrequent. In broth, mycelium and bacillary forms occur side by side.

In some points the organism here described differs from those occurring in cases of human actinomycosis of which I have found records. Those approaching it most closely are described by Foulerton ('Trans. Path. Soc.,' 1902), Bruns ('Cnt. für Bakt.,' 1899, vol. xxvi), and Norris and Larkin ('Journ. Expt. Medicine,' vol. v). Foulerton's organism was an obligatory aërobe, and it did not grow on potato. Small differences also were noted in the growth in broth. Bruns's streptothrix grew on gelatine, though slowly; growth on agar was yellowish in colour and spread over the surface. It also was an obligatory aërobe. The resemblance to the organism described by Norris and Larkin was more close, but small differences between the two occur in growth on several media and in their pathogenicity to guinea-pigs.

April 21*st*, 1903.

42. *Endotheliomata of the salivary glands.*

By RAYMOND JOHNSON and T. W. P. LAWRENCE.

[With Plate III.]

No originality is claimed for the opinions expressed in this paper; but, in view of the fact that the matter with which it is concerned is still under discussion, we feel no hesitation in bringing it to the notice of the Society, and are prompted to do so chiefly in the hope that an expression of opinion on the subject may be obtained.

The tumours with the structure of which we are concerned are the well-known "parotid tumours" and others of precisely similar character which occur in association with the other salivary glands, and in their neighbourhood—as, for instance, certain tumours met with in the palate. On account of its much greater frequency, most of the features, both clinical and pathological, of this group of tumours have been studied in the "parotid tumour," but the characters of the others above mentioned are in every respect so identical that for purposes of description they may all be included in one group. The ordinary clinical features of these tumours need not be described in any detail; it will be sufficient to remark that they are usually, in the early stages at any rate, slow in growth and distinctly encapsuled, so that they can more or less readily be removed by enucleation without the removal of any part of the salivary gland in relation with which they lie.

The tumours of this group were long described as being of a mixed structure, and were regarded essentially as adenomata—the glandular structure being combined with a stroma, which might present varying combinations of fibrous, myxomatous, cartilaginous, and sarcomatous tissue, and modifications due to degeneration of the same. For many years there has been doubt in the minds of some pathologists as to the correctness of this view, and in the abundant literature of the subject there will be found many writers who reject the view that the tumours under consideration are adenomata. Thus, as early as 1859,

Billroth (Virchow's 'Archiv,' Bd. xvii, 1859, p. 357) expressed the opinion that they were not connected with the gland acini, but arose from the capsule. A useful historical *résumé* of the alternations of opinion on this subject, and the various names which have from time to time been applied to these salivary-gland tumours, will be found in a paper by Küttner on "Tumours of the Submaxillary Salivary Gland" ('Beiträge zür klinischen Chirurgie,' Bd. xvi, 1896, p. 181). Perhaps the most important communication on this subject which has appeared in recent years is that of Rudolf Volkmann, "Ueber endotheliale Geschwülste" ('Deutsche Zeitschrift für Chirurgie,' Bd. xli, 1895, p. 1), in which the author takes the view that these tumours are endotheliomata. Thus opinions have chiefly varied between the two views—one that the most characteristic element of these tumours is epithelial, the other that it is connective tissue in origin; or, to define the position more clearly as it at present stands—is the so-called "parotid tumour" (and the others of like nature) an adenoma or an endothelioma? Our paper is offered as a contribution towards the solution of this question. The investigation comprises chiefly the examination of the series of tumours preserved in the Museum of University College; and the result of our investigation is that in none of these specimens could we convince ourselves of the presence of an adenomatous structure. On the other hand, we regard the structure which has usually been regarded as adenomatous as being really of connective-tissue origin, and we feel satisfied, from the evidence before us, that the view that these tumours are endotheliomata is fully justified. The following descriptions include the essential clinical features and histological characters of the series of tumours upon which our communication is based.

Specimen I (Univ. Coll. Museum, No. 1494).—A small solid tumour, 2 cm. in diameter, which was removed from the superficial part of the left parotid gland, in which it was embedded. The tumour is lobulated and invested by a thin fibrous capsule. The cut surface is uniform, and opaque white in colour. The patient was a woman aged 21 years; the tumour had been noticed for eighteen months.

Microscopic structure.—The stroma is in most parts finely fibrillated, and contains small oval or spindle-shaped cells; in some parts the stroma is almost hyaline and the cells scanty. Intimately

associated with the stroma there is an abundance of cells, which from a more or less spheroidal form have become in many parts, by mutual pressure, cubical or polygonal. A striking feature in the arrangement of these cells is that in many places they are disposed around well-defined spaces, containing a coagulated fluid. The spaces are tubular, being circular in transverse and cleft-like in longitudinal section; they branch and communicate one with another. The spaces are surrounded by one or more layers of the spheroidal cells above mentioned, and it is noticeable that these are intimately united with the stroma, and show no tendency to shrink away from it. From the cell-layers surrounding the spaces solid columns of similar cells pass irregularly into the surrounding stroma, the columns branching and uniting freely so as in many parts to assume a distinctly plexiform arrangement. In some areas the stroma between the columns is so scanty that the latter lie in such close apposition as to produce the appearance of an almost solid cellular mass.

Specimen II (Univ. Coll. Museum, No. 1495).—A very lobulated solid tumour, nearly 5 cm. in its greatest diameter. It is invested with a thin capsule, and its cut surface has a slightly mottled appearance. The tumour was removed from a woman aged 35 years; it occupied the parotid region and was of slow growth.

Microscopic structure.—The ground substance is very finely fibrillated, or nearly hyaline; the cells of the stroma are scanty, small, and angular or branched. The essential cell-elements of the tumour have a plexiform arrangement in the stroma, the network being formed by the irregular branching and union of the strands of cells. The cells composing the strands have an abundant protoplasm and a large rounded nucleus; they are irregularly arranged, and there is no sharp line of demarcation between the cells and the stroma. In the centre of many of the cell-columns definite spaces are present, containing coagulated granular material and surrounded in some instances by a single layer of flattened cells. In those parts of the tumour in which the cells appear to be arranged in large solid masses, instead of in plexiform strands, careful examination shows that the apparently solid mass is composed of closely packed narrow strands, the distinction between which is indicated by the presence of small, darkly staining, angular

[illegible]

Specimen III (Univ. Coll. Museum, No. [illegible]).—A solid [illegible] tumour, nearly [illegible] in diameter, covered with a [illegible] capsule of connective tissue. In the recent state the cut surface of the tumour was nearly white, in some parts opaque and in others more translucent. The tumour was removed by Mr. G[illegible] from a young man who had also tuberculosis of the right testicle. The tumour was situated in the middle of the right cheek, and had been growing for about five years; it was easily enucleated, and its posterior border lay in contact with an apparently normally large sub-parotidis.

Microscopic structure.—The stroma is abundant, and consists in all parts of a delicate, open, fibrillated network, containing small branched cells. Fibrous septa, containing blood-vessels, penetrate the growth. The essential tumour-cells have abundant protoplasm and round or oval nuclei, which stain deeply with hæmatoxylin. In different parts the cells are arranged in the following ways:—*a* Small solid groups or strands, sometimes appearing to be directly continuous with the branched cells of the stroma; *b*, larger cell-masses; *c* cell-masses with a small central lumen; and *d*, well-defined spaces surrounded by one or more layers of cells. In some of the spaces bud-like extensions of the bounding cells pass into the stroma.

Specimen IV (Univ. Coll. Museum, No. 1496).—This specimen has already been described in the forty-eighth volume of the 'Transactions' by Mr. C. F. Beadles, as a myxomatous tumour of the submaxillary gland. It consists of a solid encapsuled tumour, to one surface of which a piece of the submaxillary salivary gland is attached.

Microscopic structure.—The stroma is in most parts finely granular, apparently myxomatous; in other parts it is hyaline and contains encapsuled cells closely resembling cartilage cells. The arrangement of the essential cells of the tumour agrees with that of the last specimens in being in parts plexiform and elsewhere in the form of large cell-masses composed of closely

packed strands. It differs, however, in the absence of any tendency to the formation of well-defined spaces.

Specimen V (Univ. Coll. Museum, No. 1499).—A lobulated encapsuled tumour, 4·5 cm. in diameter. It consists of very soft gelatinous tissue, divided into separate lobes by denser fibrous bands. The tumour was removed from a woman aged 38, and had been slowly growing, without causing pain, for five years. It was situated in front of the left ear, and was easily enucleated.

Microscopic structure.—The stroma consists of a delicate myxomatous tissue with branching cells, and intersected by septa of fibrous tissues. The most characteristic feature of the essential structure of the tumour is the presence of well-defined rounded spaces (probably the transverse sections of tubes), which in many parts are so numerous and so closely packed as to produce a cavernous structure bearing a striking resemblance to that of a cavernous angioma. The spaces are surrounded by one or two layers of small flattened cells. In other parts the spaces are more widely separated by collections of cells similar to those which surround the lumina. From these cell-masses irregular strands extend into the surrounding myxomatous tissue and become intimately mixed with the branched cells of the latter.

Specimen VI (Univ. Coll. Museum, No. 1500 A).—A solid, lobulated, encapsuled tumour, 4 cm. in diameter. The consistence is firm, and the cut surface presents a mottled appearance, caused by a mixture of yellowish areas with others which are bluish white and semi-translucent. The tumour was removed from the right submaxillary region of a boy aged 16; it had been growing for eighteen months.

Microscopic structure.—The stroma is in most parts hyaline, and the cells encapsuled so as to present a striking resemblance to hyaline cartilage; in other parts the stroma consists of fibrous tissue. The tumour-cells are small and arranged very irregularly, in some parts showing a tendency to lie in strands or columns, and in other parts forming large uniform cell-masses. A disposition of the cells around spaces is here and there seen.

Specimen VII (Univ. Coll. Museum, No. 1498).—An ovoidal lobulated tumour, 11 cm. in its longest diameter, removed from

the left parotid region of a man aged 37. A strip of skin, including a scar, is adherent to one aspect of the tumour, but in the rest of its extent the surface is covered with a fibrous capsule. At one end of the specimen a large cyst, partly filled with friable tumour substance, has been opened. The section of the tumour shows a small amount of fibrous tissue, especially in its central part. The history showed that at the age of twenty-two a small movable tumour was noticed behind the left angle of the lower jaw; six years later the tumour had reached the size of a small orange and was removed. Two months later a lump was noticed beneath the scar, and steadily increased in size until it was removed by Mr. Heath nine years after the first operation. The removal was easily effected, chiefly by enucleation with the finger.

Microscopic structure.—The stroma is partly myxomatous and partly fibrous. The disposition of the tumour-cells takes the following forms:—(*a*) Solid columns branching through the stroma and intimately connected with it; (*b*) tubes, sometimes lined with a single layer of flattened cells, sometimes with two or more layers, the cells of the innermost layer being flattened; and (*c*) large collections of columns or tubes, closely packed and separated only by narrow fibrous septa. Many of the spaces are filled with a hyaline substance.

Specimen VIII (Univ. Coll. Museum, No. 1497).—A lobulated tumour, 8 cm. in its longest diameter, removed from the parotid region. The tumour is invested with a fibrous capsule which at one part has been ruptured during its removal. The cut surface of the tumour presents opaque yellow areas separated by smaller areas of a grey, semi-translucent appearance.

Microscopic structure.—The stroma consists of an irregular mixture of fibrous tissue and myxomatous tissue, which has undergone a hyaline transformation. The essential cell-elements of the tumour are very abundant, and in many parts are arranged in large collections in which no clear indications of columns or tubes can be recognised. From these large collections a direct continuity can be traced with irregular columns and threads of cells having a plexiform arrangement in the stroma. A transition can also be traced from solid cell-masses into tubes, which in some parts produce a distinctly cavernous structure.

Specimen IX (Univ. Coll. Museum, No. 1510).—A small oval

tumour, which was removed from the hard palate, together with the portion of mucous membrane beneath which it lay loosely encapsuled. The substance of the tumour is firm, almost homogeneous, and traversed by irregular clefts. The tumour was removed by Mr. Heath from a woman aged 48; there had been a small lump in the hard palate since childhood. During two years the tumour had been increasing in size; it was not connected with the bone, and was easily enucleated.

Microscopic structure.—The stroma is represented by a hyaline substance in which very few connective-tissue cells are present. The hyaline substance is arranged in narrow irregular trabeculæ or larger rounded masses, in which a faint concentric marking is sometimes seen. The irregular spaces between the trabeculæ of the stroma are filled with spheroidal cells; in some parts these cells are arranged in several layers around a distinct lumen; in other parts they form solid and irregular columns. By the close apposition of such tubes or solid columns, large areas composed almost entirely of cells result, the stroma being represented only by narrow hyaline trabeculæ.

Specimen X (Univ. Coll. Museum, No. 1500 B).—Part of a recurrent tumour of the right parotid region. The primary tumour slowly attained a large size after twenty years' growth, and was removed by Mr. Heath when the patient, a woman, was 52 years of age. Several subsequent operations were performed for recurrent growths, the tumour preserved in the specimen being removed seven years after the first operation.

Microscopic structure.—The stroma is scanty and hyaline, and in most parts is intersected by irregular columns and strands of small cells, producing a striking plexiform arrangement. In some parts the cells have proliferated to such a degree as entirely to destroy the plexiform arrangement, thus producing uniformly cellular areas of sarcomatous appearance.

From a general consideration of these histological descriptions it is evident that each tumour consists of a stroma, in which lie what we have spoken of as the essential cell-elements. The character of the stroma is of secondary importance in determining the nature of the tumours, but it may conveniently be considered in the first place. We find that the stroma most commonly agrees in character with what is usually regarded as

myxomatous tissue. It consists of a delicate tissue, which in hardened specimens presents the appearance of a network of very delicate fibrillæ, the interstices of which are filled with mucin, whilst the cell-elements are scanty, small, and irregularly branched. Mixed with the myxomatous tissue is always seen a varying amount of ordinary fibrous tissue which may be very cellular. A modification in the appearance of the stroma is due to hyaline degeneration of the fibrous tissue, the change being either diffuse, or so disposed as to produce definite rounded hyaline nodules. In some parts in which the stroma is completely hyaline the cells are distinctly encapsuled, and thus an appearance like that of hyaline cartilage is produced. Whether or not this form of stroma is actually cartilaginous we feel uncertain, and have not felt qualified to apply such chemical tests as might afford a solution of the question.

Intimately connected with the stroma are seen the essential cell-elements of the tumour. The cells themselves are usually small, and spheroidal or polyhedral, and do not present features which in themselves would indicate whether they are of epithelial or connective-tissue origin—an important question, which must be answered rather by a consideration of the relations of the cells to the stroma, than of the individual characters of the cells themselves. A feature common to all the tumours is that the cells are arranged in comparatively slender strands, some of the finest of which form threads not more than two cells thick. The larger columns appear on transverse section as rounded cell-masses. Many of the strands, instead of forming a solid column, contain a lumen, which in longitudinal section appears as a solid tube and in transverse section as a circular space surrounded by one or more layers of cells, and regarded by those pathologists who believe that these tumours are glandular as an acinus. In many cases the cells forming the layer next the lumen are flattened and endothelium-like, whilst outside this layer the cells have the usual spheroidal or polyhedral form. The contents of the spaces, when present, appear as a finely granular, or hyaline, probably coagulated material. In more than one specimen the arrangement of comparatively large spaces in close apposition produces a cavernous structure suggestive of that of an angioma.

In some cell-columns the central lumen appears only to be

present at intervals, the column being in parts tubular and in parts solid. The cell-threads frequently branch off from a larger column, and by the junction of neighbouring threads a distinct plexiform arrangement is often produced.

A common appearance in parts of all the specimens is the arrangement of cell-threads and columns in close proximity one to another, with only a slender strand of connective tissue with small nuclei passing between them; such an arrangement produces when only slightly magnified an appearance like a solid mass of cells. Less commonly the plexiform arrangement can be traced into a uniformly cellular area in which the arrangement of the cells in threads or columns is lost.

In only one specimen, a tumour of the submaxillary region, have we met with any tendency to the formation of concentric nest-like bodies in the cell-columns.

In observing the actual relation of the cell-masses and columns to the stroma, it is noticed that in some parts the line of contact between the two is even and well defined, but only exceptionally do the cells shrink away from the stroma in the process of hardening. In most parts, however, the line of contact between the cell-masses and the stroma is uneven and ill-defined, and it may sometimes be difficult to decide whether certain cells belong to the periphery of the cell-mass or to the stroma. This relation is, we think, sufficiently clearly marked to indicate the connective-tissue origin of the essential cells.

Having arrived at this conclusion, an interesting question, but one of secondary importance, arises. Do the tumour-cells originate in ordinary connective-tissue cells, or in some specialised form of the latter, such as endothelium? We agree with those pathologists who regard the tumours under consideration as endotheliomata. Our reasons for this conclusion are that the cells are arranged in definite strands, in parts often tubular, and in their general arrangement imitate an embryonic vascular formation, which may be regarded as the type upon which the structure of the tumour is based. We have not succeeded in tracing any connection between the cell-strands and normally formed vessels, nor should we expect to trace such a connection if the tumour preserves throughout its embryonic type.

The supposition appears to us justifiable that, inasmuch as normal endothelium bears close resemblances to normal epithe-

lium, so pathologically the same resemblance would be maintained. In many respects there is no doubt that the essential cell-elements of these tumours bear a close resemblance to epithelial cells in their arrangement; thus they form well-defined masses and columns embedded in a connective-tissue stroma and spreading into the latter in the form of delicate branching threads. Therefore, judging by analogy only, it seems to us that the characters of the cell-elements indicate an origin in some form of surface cell rather than in ordinary undifferentiated connective-tissue cells—as, for instance, in the endothelial cells of blood-vessels or lymphatics. We cannot bring forward any histological evidence to show whether the cells originate in the endothelium of lymphatics or of blood-vessels.

We may here incidentally remark that on histological grounds alone the question of these tumours being typical adenomata can scarcely be seriously discussed, for the structure is so essentially atypical that, if of epithelial origin, it could only be carcinomatous. We realise that the substitution of the connective-tissue theory for the glandular theory of these salivary-gland tumours raises a difficulty. On the glandular theory it is easy to explain their occurrence in the immediate vicinity of the salivary glands, and the tumours of like structure in the palate may be included in this remark. If, however, the tumours are not glandular, some satisfactory explanation is required of their very definite and limited distribution. We cannot offer any clear solution of this question, but, suspecting that the tumours have some definite anatomical origin, we venture to draw attention to the following considerations:

There is in the neck a well-known anatomical structure, the so-called carotid gland or carotid nodule, and it is of interest to note that the nature of this body has been subject to a discussion similar to that which has arisen in connection with the salivary-gland tumours. Is it of glandular origin or of vascular origin? Following Luschka, the carotid nodule has usually been regarded as a glandular structure, and to owe its development to the epithelium of a branchial arch. Later investigations, especially those of Katschenko and Marchand, have shown that the "gland" is developed independently of the branchial epithelium, and that its cell-masses are directly connected with the carotid

[illegible] ARTICLE III

[illegible] Rayleigh [illegible]
Mr. T. E. P. [illegible]

[illegible] preparation [illegible] The [illegible]
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[illegible] [illegible] [illegible]
[illegible] [illegible] [illegible]

[illegible] of the [illegible] [illegible]
[illegible] [illegible] [illegible]

[illegible] [illegible] [illegible]
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[illegible] [illegible] [illegible]
[illegible] [illegible] [illegible]

[illegible] Mr. T. E. P. Lawrence

Fig. 1.

Fig. 2.

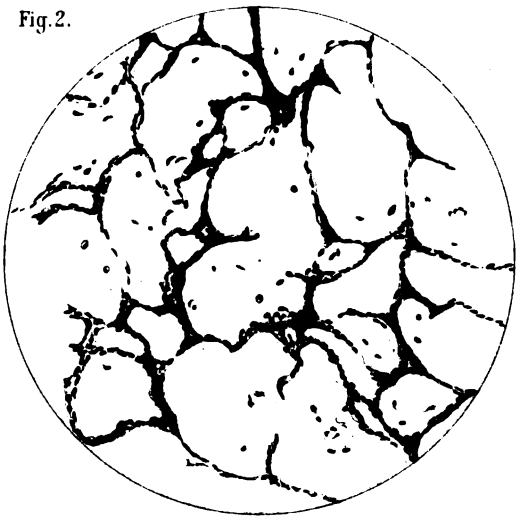


Fig. 3.

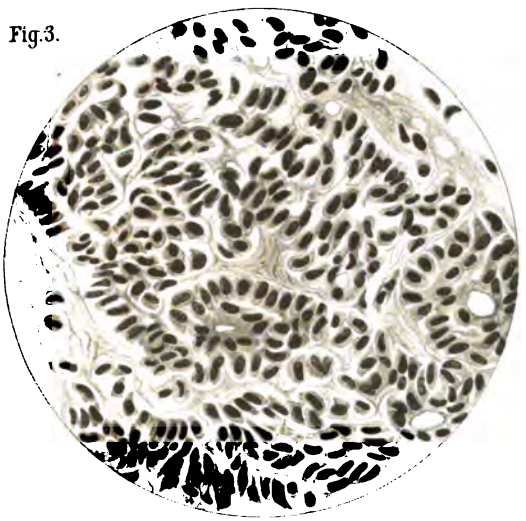


Fig. 4.

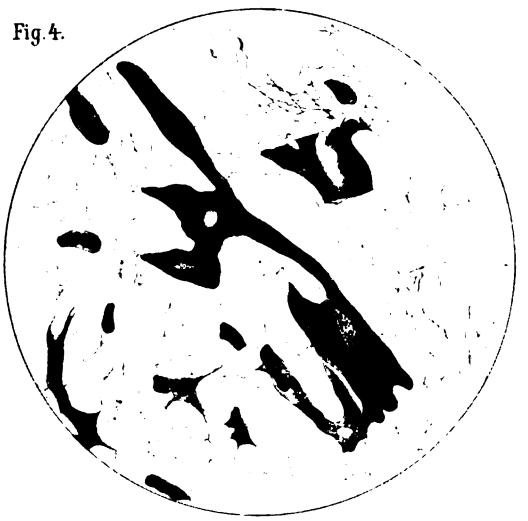


Fig. 5.

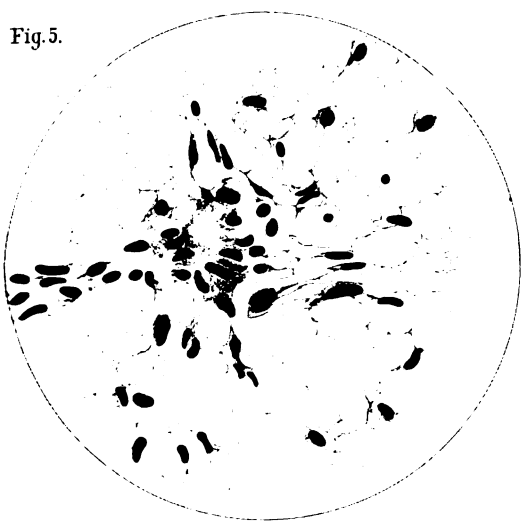


Fig. 6.

Lith. Anst. v. E. A. Funke, Leipzig.

[illegible] BRITTON [illegible] LAVELLE

[illegible]

[illegible] of the pestilence. The [illegible] [illegible] [illegible]

Fig. 1.

Fig. 2.

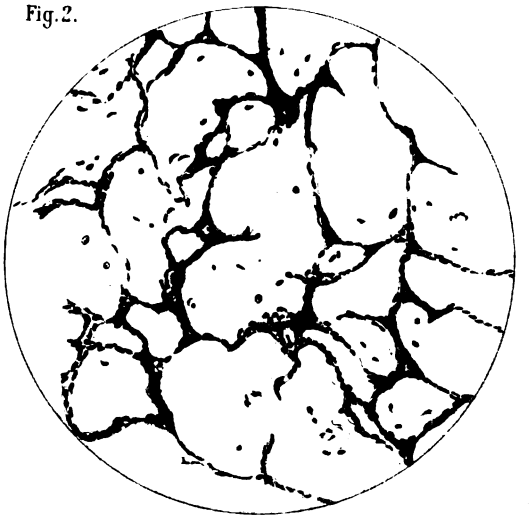


Fig. 3.

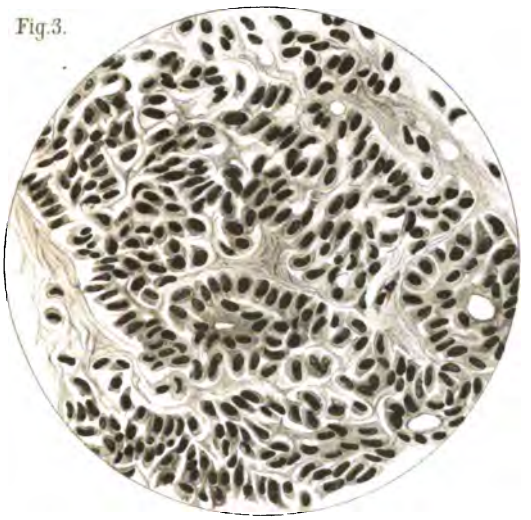


Fig. 4.

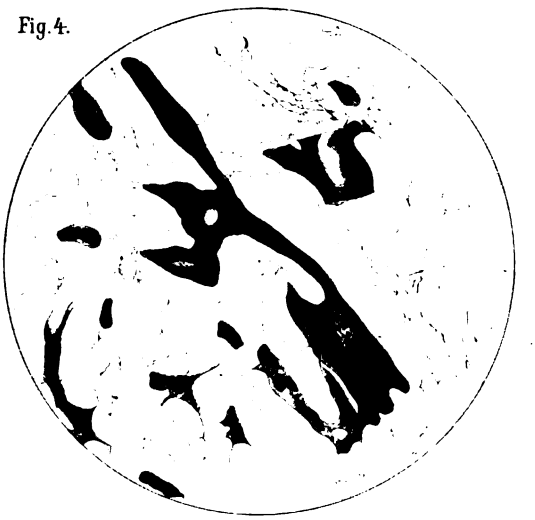


Fig. 5.

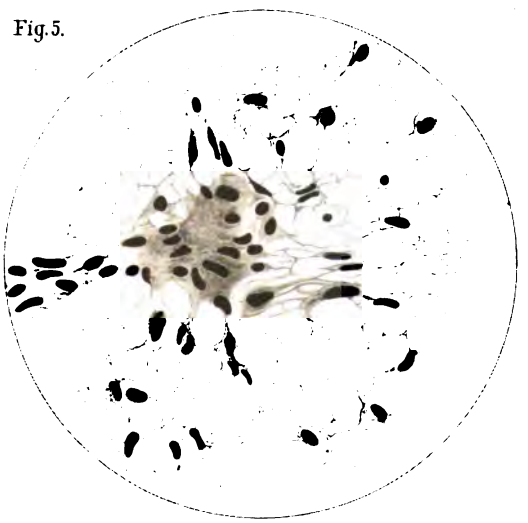
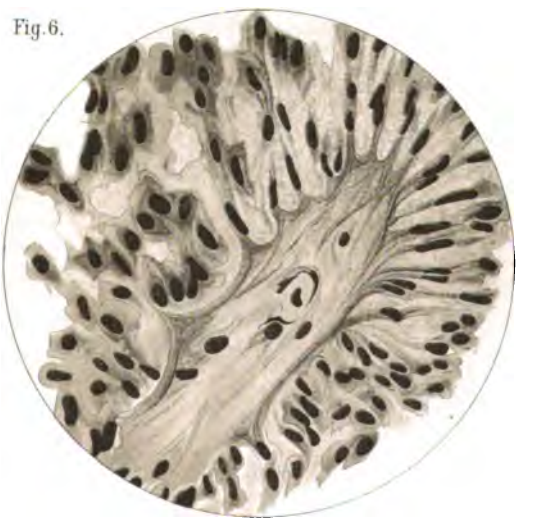


Fig. 6.



Lith. Anst. v. F. A. Funke, Leipzig

artery. There are on record a few cases of tumour-formation in the carotid gland. Ssinjuschin, writing in 1901, found seven cases in literature. In Marchand's case ('Internationale Beiträge zur wissenschaftlichen Medicin,' 1891, Bd. i, p. 537) the tumour, as large as a hen's egg, was removed from a woman aged 32, and was subjected to a most careful examination. Although at the commencement of his investigation Marchand had decided in favour of the epithelial nature of the growth, he subsequently abandoned this view and definitely decided that the tumour was of connective-tissue origin. Marchand intentionally avoids giving the growth a definite name, but he evidently inclines to the view that it originates in the vascular structure of the carotid nodule. That the tumour actually grew from the latter seems quite certain, and from the figures and description of the structure of the tumour its close resemblance to that of the salivary-gland tumours is very striking.

From this it is evident that there is in the neck at least one recognised anatomical structure capable of giving rise to tumours apparently identical in structure with those under consideration; and we venture to suggest that there may be in other parts of the distribution of the carotid arteries similar but hitherto unrecognised vascular formations, from which the tumours in question arise.

Although no obvious resemblance exists between a salivary-gland tumour and a nævus, yet, if the former is an endothelioma, the two are not pathologically widely separated. The endothelioma may be regarded as an atypical or embryonic vascular growth, and the angioma as a typical vascular growth; and it is of interest that all forms of angioma are particularly common in the area of distribution of the carotid vessels.

April 29th, 1902.

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43. *Specimens of endothelioma.*

By C. G. Seligmann.

On September 24th, 1901, a married woman, aged 31, was admitted into St. Thomas's Hospital under the care of Mr. Pitts,

to whom my thanks are due for allowing me to record the case. She was childless, and her previous history was unimportant save that in October, 1900, Dr. Swaine, of Bristol, removed her left ovary, which had become cystic. About the beginning of August, 1901, the patient's clothes felt tight across the abdomen, and three weeks later she noticed a swelling of the right side, which was and always had been painless. *Per vaginam* the uterus was displaced backwards and to the left by a tumour the size of a cocoa-nut. This was considered to be a multilocular cyst of the right ovary.

On opening the abdomen Mr. Pitts found a mass the size of a cocoa-nut in the mesentery near its lower attachment, and separating its layers. The mesentery was incised, and a large amount of soft vascular growth was enucleated. This, though fairly firm in parts, appeared not unlike placental tissue. The vascular supply of the growth appeared to come from the mesenteric vessels, which were considerably dilated. Another tumour of the same nature, about the size of two fists, was present in the mesentery higher up, enlarging the triangular space at the attachment of the bowel, and partially surrounding but not invading the latter. No enlarged glands were to be seen or felt, nor were there any signs of invasion or inflammation of the peritoneal surface of the mesentery. The ragged cavities left by enucleation of the growths were obliterated by sutures.

The patient did well after the operation, and complained of no symptoms until early in January, when a mass which rapidly increased in size was detected in the abdomen, lying beneath but not adherent to the scar of the operation wound. This caused repeated attacks of severe pain, but no obstruction; *per vaginam* the mobility of the uterus, which lay backwards and to the left, was greatly impaired. In the left fornix and Douglas's pouch a hard craggy mass could be felt which appeared to be continuous with the abdominal tumour. The lower part of the uterus was distinct from this mass, but above and to the right it was closely connected with it, so that any movement imparted to the one was transmitted to the other. The left side of the pelvis was free; on the right side, and slightly bulging into the vagina, there was a hard mass connected with that in the abdomen.

The patient left London and was attended until her death, on

February 17th, by Captain E. P. Hewitt, R.A.M.C., who has kindly supplied the following information. The mass increased greatly in size, but never became adherent to the abdominal wall; acute obstruction did not occur, and no blood or pus was passed *per anum* or *vaginam*, nor was there any trouble in micturition. There was a small amount of free fluid in the abdomen, and four days before death œdema of the left leg appeared. During the last week of life there was constant vomiting, and large quantities of bile were brought up; the patient also had several attacks of heart failure and severe pain in the præcordial region. As far as could be ascertained clinically, the liver and lungs were free from growth. No *post-mortem* was allowed.

Microscopical examination.—Under a low power the greater part of the tumour appears to be made up of irregular columns and groups of cells, between which there is a small amount of loose connective tissue. Here and there are spaces bounded by more or less rounded cells, which appear to be of the same nature as those constituting the mass of the tumour. Into these spaces, which contain the remains of a granular coagulum, a few simple papillary processes project, suggesting that the fluid which filled their cavity during life was not under any great tension.

With a higher power the cells bounding the spaces are seen to be more or less spheroidal, and for the most part to form a layer one or two cells thick. In places, however, these cells extend more deeply into the underlying stroma, and direct continuity can in many places be traced between the cells forming the walls of the cavities and the columns of cells which form the chief feature of the tumour. In many of the cavities, especially in the smaller ones, the border of the cells bounding the space appears cuticularised, and takes the stain more deeply than the other parts of the cytoplasm.

There is no proper basement membrane in the usual sense of the term, though in places the connective-tissue cells form an incomplete bounding line beyond the cell-layer referred to.

There are also a number of spaces lined with a single layer of flattened epithelium; these contain blood-corpuscles, and are hence easily differentiated from those already described, which are probably lymphatic in origin, the growths themselves representing the result of proliferation affecting subperitoneal

lymphatics near the root of the mesentery. There is nowhere any sign of inflammation or infiltration with leucocytes.

The other tumours are both from the palate. The first of these, an encapsuled growth about the size of a walnut, occurred in a man aged 56, who gave a history of six months' duration. In April, 1901, a dentist put a seton into a "pustule" on the inner side of the alveolus of the upper jaw, and extracted a tooth. The swelling, which had first been noticed in March, increased in size until October, when Mr. Clutton found an "elastic swelling extending over the hard palate, with a small ulcer towards the alveolus, which was not itself involved." The tumour was removed without sacrificing the hard palate or remaining teeth; the ulcer on its surface did not extend into its substance, and appeared to have been caused by the dentist's seton. In April, 1902, there had been no recurrence.

The main part of the tumour consists of masses of more or less spheroidal cells supported by a varying amount of intercellular material which has undergone a hyaline change. In places it is clear that this change has affected the original fibrous supporting tissue of the tumour; in other parts various stages of degeneration of the spheroidal cells above alluded to can be traced into the completely degenerated areas, and it seems as if these were, at any rate in part, made up of tumour-cells which have become hyaline. Throughout the tumour—where the arrangement is not obscured by the enormous growth of cells—are to be seen branching and anastomosing spaces almost certainly lymphatic in origin, which are lined with a varying number of layers of cells, which in places are in direct continuity with the groups of cells forming the main mass of the tumour. These lining cells, which tend to be spheroidal, are here and there markedly columnar; indeed, practically all transitional forms between columnar and spheroidal cells can be observed. Active proliferation of the endothelium appears to be taking place, and in many sections karyokinetic figures can be seen.

The remaining specimen, also removed by Mr. Clutton, whom I take this opportunity of thanking for allowing me to make use of his cases, occurred in the soft palate of a married woman aged 43. She had noticed the tumour for two years, during which time it had been slowly growing. She suffered no inconvenience from it until shortly before operation, when its

surface ulcerated; this she thought was due to its having been scratched by a hurriedly swallowed piece of crust. She was operated on in March, 1901. The growth was not obviously capsulated, and it is possible that outlying portions were left behind. Recurrence has taken place, and at the present time there are two small, flat, raised masses in the soft palate in the immediate neighbourhood of the scars left by the previous operation.

The original tumour, which was extremely soft and gelatinous, had no definite capsule. Microscopically it consists of a loose fibrous stroma, in which there are embedded cellular masses which are in general roughly cylindrical. The cells themselves are spheroidal, with well-stained nuclei. Most of the cellular masses are not solid, but contain a central lumen with a well-marked basement membrane, internal to which there is a rough network of coagulated proteid. Since none of these spaces contain corpuscles or anything suggesting blood-clot, they may be looked upon as lymphatic in origin, and the columns of cells as filling and distending connective-tissue spaces. Everywhere in the substance of the cell-masses there are many small areas of a faintly granular hyaline substance, formed by the degeneration of groups of cells which contrast sharply with those unaffected. A similar change has in places taken place in the supporting stroma to a slight extent, and where it has affected large groups of cells has given rise to coarsely reticulated, structureless tracts, scattered about which there are a few undegenerated cells and polymorphonuclear leucocytes.

In conclusion, it would seem that both the palatal tumours result from the proliferation of lymphatic endothelium. In the first case it appeared as if the endothelium lining every connective-tissue cleft took an active part in the process; in the second, the process appeared more limited. *April 29th*, 1902.

The history of both the cases of palatal tumour since the above was written seems to be worth recording. The first case presented a minute ulcer near the posterior margin of the hard palate. This was excised, as owing to the pressure of a plate it caused discomfort. Microscopical examination showed that the ulcer was the result of inflammation of a mucous follicle, perhaps

caused by the pressure of the plate. The second case was seen in July, when it was noted that one of the flattened raised masses had ulcerated. Both masses were freely removed, together with the intervening mucosa. Microscopically the tissue consists of compact irregular masses of cells of considerable size, separated from each other by a larger or smaller quantity of loose connective tissue. Some of these masses are roughly cylindrical, others are crescentic or irregular in outline, the appearance of the whole suggesting that they have exercised a considerable amount of mutual pressure. A thinning of the palatal epithelium, visible in places, and not due to direct extension of the tumour-cells, may be attributed to the same cause. Each mass consists of more or less spheroidal cells with deeply staining nuclei, among which there are numerous non-cellular areas, for the most part circular or oval in outline and remarkably regular in distribution, which appear to have been formed by the degeneration of groups of cells of which the tumour is composed. These areas are filled with a finely granular or fibrillated material, which in the smaller spaces is fairly dense, but in the larger is irregularly vacuolated. In places the spaces produced by degeneration are less regular in outline, having in fact no very definite form, and suggesting at first sight an irregular series of channels which here and there have a branching or moniliform appearance. The inner edge of the cells bounding most of the spaces is sharply defined, but in some spots this appearance is absent, and it can then be clearly seen that the spaces have originated by degeneration directly from the cells of the tumour. At one spot a number of cells with well-defined nuclei lie in the centre of such a space surrounded by and fusing with the fibrillated material already referred to, which in turn is bounded by the sharply defined walls of cells surrounding the space. As in the original tumour, a large part of what at first sight appears to be stroma is composed of strands and irregular groups of more or less degenerate and vacuolated cells, which in many places are in direct continuity with the more irregular cell areas of the tumour.

November, 1902.

44. *A mixed tumour of* (1) *lip, and* (2) *of the submaxillary gland, probably endothelial in origin.*

By EDRED M. CORNER and S. GEOFFREY SCOTT.

THE tumour was removed from the upper lip of a student of St. Thomas's Hospital. He was twenty years of age, and had had the tumour as long as he could remember. It had increased in size but slowly, and had given rise to no pain. It was freely movable, and was easily removed from the mucous membrane of the lip under eucaine anæsthesia. Owing to its size and liability to injury he had desired its removal. The glands in each lip could be felt as shotty masses, but were not larger than usual.

After removal the tumour was rounded and encapsulated, about 3 cm. in length and 2 cm. in diameter. Thin slices of it were cut shortly after the operation and placed in Ulann's picro-corrosive fixative. Sections, 5 μ thick, were cut and mounted on albumenised slides, and then stained by various methods. Under a low power, Zeiss A A and 6 compensating ocular, the tumour was seen to be completely surrounded by a capsule, over one part of which a mucous gland is stretched, a few acini being embedded in the outer side of the capsule. The mass of the tumour is seen to consist of two main elements, a supporting tissue and a parenchyma. The supporting tissue consists of islands of cartilage, which gradually change into a fibrillar stroma having no distinctive arrangement. Where the supporting tissue is absent, a parenchyma is seen composed of dense masses of cells, studded with spaces of varying size and shape.

Under a higher power, Zeiss D D and 6 compensating ocular, the cartilage is seen to be fibrillar—in fact, an aggregation of the fibrils which form the general reticulum. There are not many cells present in it. Their appearance resembles that of mucoid rather than that of fibrous tissue. The parenchyma consists of closely packed masses of cells which vary somewhat in size. In shape they may be round, polyhedral, or slightly fusiform. In many places they can be seen, under 2 mm.

apochromatic, to be joined to each other by protoplasmic bridges. From the angles of some of them fine processes start off, soon to become lost amongst the surrounding cells. The nuclei vary much in size, in some cases occupying a large part of the cell, and in others proportionately far less. No signs of degeneration can be seen, nor is there any evidence of active growth.

In the parenchyma may also be seen spaces of various sizes and shapes, some of which contain a granular coagulum. At the edge and outer part of the section, however—that is, in the best fixed part,—a few of these spaces are seen to contain red blood-corpuscles in masses, whilst others contain these along with the above-mentioned coagulum, thereby suggesting that this coagulum is broken-down blood. Structurally the spaces are not separate tubes lying in the parenchyma, but seem to be canalisations of it. Some of them are lined by a flattened endothelium lying directly on the underlying cells of the parenchyma, and others are lined with cubical cells directly continuous with those of the general parenchyma. In others the lining is of a mixed type, consisting of flattened endothelium, the cells of the parenchyma flattened on their free surface, and finally cubical, columnar, or polyhedral cells, all lying directly on the parenchyma.

This tumour was removed from the left parotid region of a man aged 39. The tumour had been getting larger slowly for eight years. It was excised on July 20th, shelling out easily, and the wound healed by first intention. We take this opportunity of thanking Mr. Clutton, under whose care the case was, and for whom we acted.

The mass removed was about 4 cm. in length and 3 cm. in breadth. Thin slices were fixed in Lurker's fluid. Two sets of sections were examined: A, without any capsule; and B, with the capsule along one corner. After embedding in paraffin, sections 5 μ in thickness were cut. Several staining methods were employed, and the best results were got from hæmatein and benzopurpurin. Under a low power, Zeiss A A with 6 compensating ocular, the tumour, beneath the capsule, is seen to consist of a supporting tissue and parenchyma, which contains strands of curious amorphous material. In sections of the tissue B a few trabeculæ of fibrous tissue are seen entering the

tumour from the capsule; in those of A there are none. The parenchyma is arranged in large masses, containing spaces of an alveolar appearance, many of which contain blood. A few finger-like processes of it are seen extending into the supporting tissue, as is so common in parotid tumours.

When examined under a high power, Zeiss 6 compensating ocular and D D or 2 mm. apochromatic, the following structure is distinguished:—The supporting tissue is seen to consist of a loose feltwork of fine fibrils coated with a granular coagulum, probably the proteids of the lymph that bathed them. Lying in this network are sparsely scattered cells, in many places like cartilage cells, which stain faintly and give rise to the fibrils of the tissue. In one or two places these fibrils are aggregated together, giving an appearance suggestive of an islet of cartilage. Except for these patches the tissue has the microscopic appearance of mucoid tissue.

The parenchyma consists of masses of closely packed cell that tend to be oval in shape with oval nuclei. In favourable places protoplasmic bridges can be seen joining a cell to its neighbours. The amorphous strands mentioned above permeate the parenchyma in every direction. They were first thought to be some peculiar form of connective tissue, but Dr. Gustav Mann, of Oxford, suggested that they were degenerated cells, and a careful examination confirmed this view; for whilst the cytoplasm of the healthy cells stains faintly with acid dyes, the strands stain deeply, and every degree of depth of staining can be followed as the cells undergo degeneration. The nuclei are the last to go, for sometimes they may be seen stained with hæmatoxylin in the midst of the masses of degenerate cells, and at others their outline may be distinguished stained faintly with the acid dye. Occasionally the outline of a whole cell, or even of several, can be seen in one strand. We have only seen one cell undergoing mitosis in our examination of the specimens. Several sections of the tissue B show cells in the capsule exactly like the parenchyma cells, an appearance reminding one of a cancer.

The alveoli are simply spaces lying in the parenchyma mass, and frequently contain blood. They are not marked off in any way from the parenchyma. The cells which line them are generally long, flattened, endothelial cells, but often, just as

in the other tumours, the lining is not completely composed of these cells, their place being taken by ordinary parenchyma cells, some of which are flattened on their free surface and some not at all. The section of the tissue A was most fortunate, as the knife in cutting it went through a large blood-space, one side of which runs for several mm. along the edge of the section. In this place the variations of the lining cells may be studied, as they are here very well fixed. In many of these spaces the degeneration mentioned above has picked out cells just behind the lining cells.

In some of the sections a very few alveoli were seen which were lined by cubical or columnar cells which rest on a basement membrane. They are very few and far between, and probably an epithelial element. They resemble closely the sections of a duct of a normal salivary gland, and in our opinion have no connection with the parenchyma of the tumour.

From a prolonged study and careful consideration of the tumours above described, we believe them to have originated in the endothelium of blood-vessels, and will very briefly enumerate the chief points on which we base our contention:

1. The structure of the walls of the spaces in the parenchyma, and the variations of their lining cells.

2. The relations of these lining cells to those of the parenchyma.

3. The presence of blood in these spaces indicates their function, and forbids their being epithelial in origin.

4. The absence of properly formed vessels in the parenchyma, of these tumours of long clinical history, and their extreme rarity in the supporting tissue.

The literature on the mixed tumours of the parotid is large and involved, and we have made no attempt to unravel it for our specimen. That of tumours of the lip is small, and has been examined. Dr. Goodhart, in the 'Trans. Path. Soc.,' vol. xxviii, p. 213, described with great care three tumours from the lips. The first was a cystic adenoma, and the second a fibroma. The third is extremely interesting, and is illustrated by the author's own sketch. It is a chondroma containing a lot of fibrous tissue, and "very little true gland tissue." Dr. Goodhart calls it a fibro-cellular tumour, and from his drawing and description there is good reason to believe that it was a tumour such as we have

described to-night. The clinical history may be briefly given as follows:—A man aged 36, giving a history of the presence of the tumour for three to four years, with slow increase of size. The tumour was $\frac{3}{5}$ inch in diameter. It was not stated from which lip it was removed. Mr. Dunn, in the same 'Transactions,' vol. xlvi, p. 190, records the removal of a large tumour from the upper lip of a young man, and terms it a fibro-adenoma, though no account of its structure is given. Mr. Robinson, in the 'New York Medical Record,' 1886, vol. xxx, p. 304, describes a tumour removed from the upper lip of a man aged 36, which was 1 inch by $\frac{3}{4}$ inch in size. The length of the clinical history was two years. The tumour is described as a "mixed tumour," but, as it was not feasible to consult the original ('Trans. American Dermatological Association,' Boston, 1886), no surmise can be made as to its origin. Similarly papers by Reverdin and Meyer[1] could not be consulted. Müller, in his 'Veterinary Surgery,' says that swellings near the angle of the mouth are found in animals, and "resemble fibromata." In nearly all works the presence of mixed tumours of the lips is not stated. Examples of these are recorded as occurring in four cases.

April 29th, 1902.

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45. *Four examples of endothelioma.*

By H. D. Rolleston and Otto Grünbaum.

As bearing on the subject of endothelioma, sections of four tumours are shown, three from the cheeks and one from the upper lip. Of these the first is a typical endothelioma free from cartilage. The second, although probably of much the same nature—namely, a perithelioma,—is also an excellent example of the group of tumours recently termed blastomata by C. Powell White,[2] meaning by this designation tumours composed of cells

[1] Reverdin published at Lille, and Meyer at Aachen, 1890.

[2] Erasmus Wilson, "Lectures on the General Pathology of Tumours," 'Lancet,' February 15th, 1902.

originally all of one type or "indifferent," eventually forming both epithelial and sarcomatous tissue. Such tumours have been called carcino-sarcoma, cylindroma carcinomatode, and adeno-sarcoma, and are illustrated by certain tumours of the kidney arising in early life.

Tumours 3 and 4 are endotheliomata resembling histologically parotid tumours; one, however, was removed from the margin of the upper lip, and the other from the cheek.

Case 1. *Endothelioma of the cheek.*

Clinical abstract.—The tumour was removed from a woman aged 35, and had been noticed for three years; it had gradually increased in size, and was tender on examination. The tumour was in the substance of the right cheek in the centre of the space bounded by the right labial commissure, the posterior margin of the ramus of the jaw, the lower border of the zygoma, and the lower border of the mandible. It was not attached to the skin or to the mucous membrane of the cheek. It was lobulated. It had no visible connection with the parotid gland.

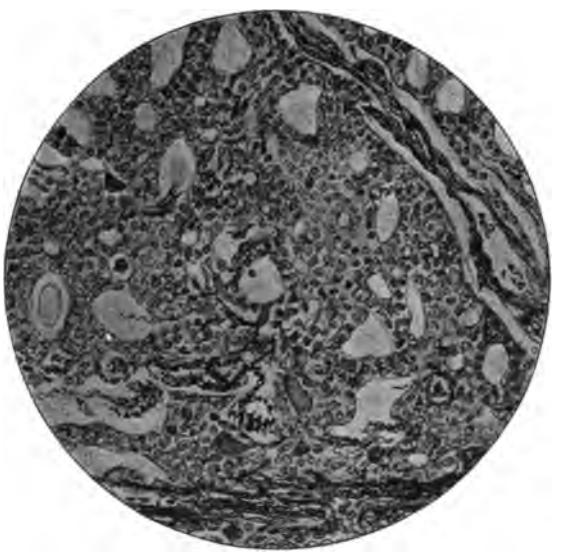
Microscopically it consists of tubules of varying complexity in a connective-tissue matrix which is undergoing hyaline degeneration. In cross-section some of the tubules are composed of two endothelial cells, and give the impression of being normal lymphatic capillaries; while others, although lined by a single layer of flat endothelial cells, are larger and dilated. It seems probable that this apparent dilatation may depend on proliferation of the lining endothelium in four directions only, and approximately in the same plane; while when this custom is lost by the cells and they multiply in six directions, tubes containing several layers of cells result. Coincident with this irregular multiplication the cells lose their characteristic flatness and assume a more or less columnar shape (metaplasia). *Pari passu* with this endothelial proliferation there is a degeneration of the connective tissue, so that in parts it is unrecognisable.

The alveolar spaces are lined by endothelial cells, and contain homogeneous non-staining material. These spaces probably arise in two ways: (1) from the accumulation of endothelial

cell secretion and degeneration; (2) by the endothelial cells growing around masses of connective tissue, cutting off their nutritive supply and causing complete disintegration and degeneration.

This latter conclusion rests upon the fact that sections prepared with the acid-orcein elastic-tissue stain are seen to contain elastic tissue in the interior of some of the alveoli. It is well known that elastic tissue offers great resistance to degenerating

FIG. 32.



Showing the structure of the tumour described in the text, and the deeply stained (acid-orcein) elastic tissue in certain of the spaces.

influences, and it seems more reasonable to assume that the rest of the connective tissue has degenerated in these spaces than to believe that the elastic tissue has been formed in them.

Case 2. *Perithelioma of the cheek.*

Clinical abstract.—A man aged 24 had had a growth on the right cheek behind and below the labial commissure for several years; recently it had grown more rapidly, and on that account he sought surgical treatment.

Microscopically the tumour is composed of a fibro-vascular

peripheral part which may be regarded as a capsule, and of a softer part which is of a villous structure.

Many of the blood-vessels in the fibrous part are surrounded by a small-celled infiltration, apparently inflammatory, but the small cells surrounding one of the large vessels resemble endothelial cells in that they are elongated, possess oval nuclei, and have their long axes radial to the vessel (perithelioma). It is tempting to assume that this is the starting-point of the growth,

FIG. 33.

Showing a blood-vessel surrounded by spindle-cells.

but no definite continuity can be established between this vessel and the rest of the growth.

The villous part of the tumour has a considerable resemblance to a villous or duct carcinoma, and is composed of two kinds of cells, presenting respectively the characters and properties of connective-tissue cells and of glandular epithelium.

The connective-tissue cells are spindles of varying length and thickness, resembling in different sites elementary endothelium, ordinary connective-tissue cells, and spindle-celled sarcoma.

It is difficult to draw a hard and fast line between the flat-

tened endothelial cells of lymphatic spaces and the sarcomatous cells, and also between oval spindle-cells and some of the epithelial cells; it is true that the well-formed columnar cells possess an affinity for the pyronin stain characteristic of epithelial cells, and appears very different from the sarcomatous cells, but transitional forms can be made out in parts of the sections. The columnar cells cover the papillary processes and in places appear to be two or three layers deep. As in villous carcinoma, so here the papillary arrangement gives rise to the impression of an alveolar formation.

The columnar cells possess large oval nuclei placed approximately in the centre of the cell, with multiple nucleoli, and present in places active mitosis. It is reasonable to think that the papillary arrangement has arisen as a result of the surface layer proliferating more rapidly than the underlying layers.

The papillæ are composed of a central core containing a lymphatic vessel surrounded by some number of layers of sarcomatous-looking cells, and these in turn are covered by columnar epithelium. The spaces contain *débris* with a few altered white blood-corpuscles.

The tumour is probably a perithelioma derived from the endothelium of perivascular spaces. Striking features are the transition from cells of a sarcomatous type to cells exactly resembling columnar epithelium, and the villous or papillomatous arrangement.

Case 3. *Endothelioma of lip.*

This tumour was removed from the margin of the upper lip of a man aged 34. He had noticed it for a year before he had it removed.

Microscopically it consists of a matrix closely resembling hyaline cartilage, containing alveoli mostly filled with large cells.

Spaces resembling lymphatic vessels run through this matrix, and are lined in some parts by flat endothelium and in others by columnar cells. These columnar cells appear to be altered endothelial elements, since it is possible to trace the transition from the flattened to the columnar form.

The individual cells forming masses in the lumina have lost,

through compression, their columnar form, and have assumed that most fitting to their environment.

The tumour is practically indistinguishable from an ordinary endothelioma of the parotid.

Case 4.

This tumour was removed from the cheek of a young woman. Microscopically it is similar to that just described.

April 29th, 1902.

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46. *Cystic adenoma of the pancreas.*

By W. Watkins Pitchford.

Alice P—, aged 29, single, a parlourmaid, was admitted to the General Hospital, Birmingham, August 2nd, 1899. She complained of a swelling in the abdomen, with pain in the bowels and lower part of the back.

Family history.—Not particularly suggestive. One uncle (maternal) and one cousin (paternal) died of "consumption."

Previous history.—Has had weak digestion for many years. This has been aggravated since the appearance of the abdominal swelling, and has been accompanied by more marked constipation.

Present illness.—First noticed an increase in size of abdomen about two years ago. The tumour has increased quite gradually, and has caused little inconvenience from its size till about five weeks ago. Her only complaints have been some increase in her dyspepsia, and pains in abdomen and back.

Condition on admission.—A well-nourished, healthy-looking woman, with a prominent abdominal tumour. The tumour is mesially placed and lies for the most part in the hypogastric region, about one third only being in the epigastric area. The most prominent point is two inches below the umbilicus, and appears as two rounded eminences, placed side by side, and separated by a median furrow. The general contour of the

tumour is ovoid, the narrow end being upward; its size is about that of a cocoa-nut. The mass is freely movable upwards and to the right, less so to the left and downwards. The edge of the hand can be inserted under the margin of the tumour all round, except below and to the right. The umbilicus is not obliterated. The abdominal walls slope downwards sharply from the summit of the tumour on either side. During inspiration the tumour does not descend, but the abdominal walls swell out and produce the appearance of diminished prominence in the growth. The tumour feels firm and largely nodular; the elasticity of the nodules varies. On the upper part of the right-hand side is a firm elastic nodule, freely movable on the main mass. The tumour is dull to percussion all over; it is surrounded on all sides by a band of resonance. Some enlarged veins are apparent in either groin.

Vaginal examination.—An elastic mass in the anterior fornix can be felt to be continuous with the abdominal tumour.

Heart and lungs.—Afford normal physical signs.

Urine.—Normal.

Character of pain.—The pain complained of in the abdomen shoots down into both legs; it is constant and of an aching character; it is worse after much standing or walking; it is relieved but not removed in the recumbent position; it is more marked when the patient lies on her back than when she lies on her side.

Operation.—Saturday, August 5th, 1899. Ether was administered. Dr. Thomas Wilson operated in the presence of Dr. Malins. The operation lasted one hour and three quarters (10.15 to 12). Median incision from near the pubes to ¾ inch above the umbilicus (the patient being in the Trendelenburg position). The uterus and both sets of appendages were found to be quite normal. The great omentum was found to be stretched out over the tumour, being lightly adherent to its more prominent parts, and passing freely over the sulci between the rounded projections. The transverse colon was found to be displaced downwards below the tumour, and to cross the abdomen near the pubes. The growth projected through that part of the great omentum which lies between the stomach and the transverse colon. The omental covering, which was much atrophied, was torn through and detached from the tumour. An attempt

was then made to make the mass present through the abdominal wound; although movable in a horizontal plane, it could not, however, be raised at all from the posterior abdominal wall. A second peritoneal investment—the parietal peritoneum of the lesser sac—was now stripped off, and the tumour was shelled out of its bed with comparative ease. The sides of the growth were found to be bound back to the posterior abdominal wall by connective tissue, which was in places thickened and fleshy-looking; clamps and ligatures were applied to these fleshy-looking bands before they were divided. One or two large veins required special care in securing. The cavity which the tumour had occupied showed a rough posterior surface, in which no definite structures could be discerned; its boundaries beyond the cut edges of the connective tissue and peritoneal investments were seen to be the stomach above and the transverse mesocolon below. The cavity remained singularly dry. The aperture in the great omentum was closed by a line of catgut sutures, and the wound in the abdominal wall by three tiers of interrupted stitches, catgut for the peritoneum and muscular layers and silk-worm gut for the skin. No drainage was used. Marked inhibition of the heart's action was reported by the anæsthetist during traction on the tumour, and the patient left the table with signs of considerable shock.

A rapid and satisfactory recovery was made; the superficial sutures were removed on the tenth day, and the patient left for a convalescent home sixteen days after the operation. In January of this year Dr. Thomas Wilson reported the patient to be in good health.

The entire growth weighed 2 lbs. 2½ oz. Its greatest diameter was placed transversely in the body, and measured 17 c.mm.; its vertical measured 8·5 c.mm. The tumour, which is of the nature of a multilocular cyst, has a common wall of tough connective tissue, the thickness of which varies from 2 mm. to 6 mm. Attached by a short and slender pedicle to the upper part of the anterior aspect is a group of three or four small cysts adherent to one another, and having evidently arisen by a process similar to that by which the main mass was formed. The tissue of the wall of the main growth is continuous throughout the whole mass with the secondary cysts in the interior, and it is evident that the growth has originated

by the cystic distension of spaces scattered throughout some more or less homogeneous tissue. In the thickness of the main wall are to be seen numerous cystic spaces, showing the greatest variations in size, but differing in no essential from the large cysts which compose the bulk of the tumour; in fact, as before stated, both the intra-mural and the large cysts of the interior have all originated in a common matrix. The large cystic spaces vary greatly in size, the largest having a diameter of about 5 c.mm.; adjacent spaces have their dividing walls in common, and this common wall is bulged by the largest cyst into the cavity of its smaller neighbour. It will be seen that in this way the cystic cavities are of an irregular shape, and have for the most part that of a hollow concavo-convex lens.

All the cystic spaces, the cavities of which were opened shortly after the growth left the body, were fully distended with liquid. Into a large cavity at the lower part of the tumour a considerable hæmorrhage had taken place at some previous though not very remote time.

The liquid from the cyst spaces had the following characters:—It was inodorous, transparent, of an olive-brown colour, and with a specific gravity of 1020. The reaction was markedly alkaline; a few crystals of cholesterin were deposited upon standing. Tests for amylolytic, fat-splitting, and tryptic properties all proved negative. The power to emulsify olive oil was not more marked than in any other solution of proteids in an alkaline medium. The liquid did not coagulate either spontaneously or upon the addition of a little blood-clot.

After neutralisation, heat-coagulation produced a precipitate amounting to from one third to one half the bulk of the sample. The proteids present were serum albumen, serum globulin, small quantities of alkali albuminate, and traces of proteoses and peptones. Nucleo-albumen was present, but neither mucin nor pseudo-mucin could be detected.

Microscopic anatomy.—The main tissue of the cyst walls consists of bundles of fibrous tissue packed in varying degrees of closeness. In the fibrous tissue are foci of more actively growing connective tissue. In some places these young connective-tissue cells appear grouped in heaps below the lining epithelium; in this way are formed low eminences, projecting into the cavity of the cyst.

The slender pedicle by which the smaller mass of cysts was attached to the main body of the tumour, proved on section to consist of two or three bands of plain muscle-fibre, surrounded by a material somewhat resembling Wharton's jelly in structure, and loosely wrapped in connective tissue. Plain muscle-fibre is also found in the bands of connective tissue which tied back the tumour to the posterior abdominal wall. The cystic spaces are lined with a single layer of short columnar cells, having well-marked nuclei placed near their basal ends. This epithelial lining is very readily detached, and is found wanting over wide areas in the larger cavities. Some sections show certain of these lining epithelial cells projecting beyond the general level towards the cavity of the cyst. In the connective tissue there occur clusters of cells of polyhedral form, and furnished with a spherical, deeply stained nucleus. A moderate number of lymphocytes also occurs in the tissue first named.

In two of the sections typical gland tissue has been encountered. In one this appears as the cross-section of a tubular structure lined with columnar epithelium and having no lumen. In the other a distinct lobulus is seen in the gland-loculi, of which the cells are of a polyhedral form, with clear cell body.

Remarks.—This multilocular cystic tumour developed behind the peritoneal covering of the posterior wall of the lesser peritoneal sac. There can, I think, be little doubt that it is derived from the pancreas being probably developed, very early in life, in some outlying fragment or accessory portion of the gland. If this theory be correct it is interesting to note that pancreatic properties were entirely absent from the cyst contents.

The simplicity of construction and the absence from the tumour of cartilage, bone, striped muscle, or skin organs, preclude, I think, the suggestions of teratoma and included fœtus. More suggestive of a pancreatic origin than mere anatomical position are, however, the characters of the traces of glandular tissue found in the specimen.

With respect to the peculiar cells in the connective tissue, it was at first a temptation to look upon them as representing the cell-islands of Langerhans. Mr. Shattock, to whom I referred the question, and to whom I am much indebted for looking through my sections and giving me many valuable hints, is inclined to regard them as plasma-cells (Unna). He

has also drawn my attention to a paper in the 'American Journal of the Medical Sciences' (vol. cxx, 1900, p. 184) by R. H. Fitz (Boston). The title of Fitz's communication is "Multilocular Cystoma of Pancreas," and a similar case is therein described, and references given to further examples previously recorded.

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47. *Polio-encephalitis inferior.*

By Frederick E. Batten.

[With Plate IV.]

A girl aged 5 years had measles and whooping-cough in April, 1902. From these affections she recovered and went to the country for a month, and returned in good health at the end of August.

She went to school at the beginning of September, but was taken ill on September 4th, and was feverish and languid. She was kept in bed, but was still feverish on the 5th, and on the morning of the 6th she suddenly developed right facial palsy, and vomited continuously. On the following morning she was admitted to the Children's Hospital, Great Ormond Street. She was quite conscious and rational, could talk and answer questions, and could perform all movements of her limbs. She protruded the tongue straight. There was complete paralysis of the right side of the face. There was no affection of the ocular muscles; the pupils were equal, reacted well to light, and there was no optic neuritis. The palate did not move well on the right side, and there was evident difficulty in swallowing the saliva. There was a history of old ear disease, but the membrana tympani was normal; there was no deafness, and no tenderness about the mastoids. There was no evidence of affection of the fifth nerve. There was no rigidity of the neck. There was no rigidity of the limbs. The knee-jerks were active, and equal on the two sides. The plantar reflexes were variable, sometimes giving extensor and sometimes flexor responses. The temperature was 102° F., the pulse 100 and irregular. The child was seen by my colleague, Mr. Kellock,

who considered it possible that the condition might be due to a subdural abscess in connection with disease of the petrous portion of the temporal bone. The skull was therefore opened above the mastoid and the petrous portion of the temporal bone explored, but nothing abnormal was discovered. The dura mater was not opened. The wound was closed. The child was somewhat restless after the operation. On the following day the child's condition was not materially altered, except that she was rather more drowsy and mucus was collecting in the larger bronchial tubes. She died on the following day of respiratory failure.

At the autopsy the skull, membranes, and brain appeared to be normal. There was no flattening of the convolution, and no evidence of any affection of the seventh or ninth cranial nerves on their emergence from the brain. The petrous portion of the temporal bone was normal, and there was no disease of the middle ear. There was no disease or thrombosis of any of the larger vessels. An incision was made separating the pons and medulla, and in the region of the seventh nucleus on the right side a deep red patch of congestion was seen. The brain, medulla, and spinal cord were hardened in formalin. No disease was found in the thorax or abdominal organs.

Microscopical examination.—Sections from various portions of the nervous system were examined by the Marchi, Weigert-Pal, Nissl, and van Giesson methods. So far as the Marchi and Weigert-Pal methods were concerned the results were negative. The cortex and substance of the cerebral hemispheres and the cerebellum appeared normal. Sections through the upper portion of the pons showed considerable perivascular exudation in the immediate neighbourhood of the vessels, but the nervous tissue appeared normal, and there was no extravasation of blood. Sections of the medulla at the level of the sixth and seventh nuclei showed considerable engorgement of vessels and perivascular exudation. The region of the seventh nucleus on the right side was completely destroyed by the exudation of small round-cells and hæmorrhage into the tissue (Plate IV, figs. 1 and 2). The nucleus of the seventh nerve on the left side appeared natural, as were also the nuclei of both sixth nerves. Although the changes were most marked in the region of the seventh nucleus on the right side, yet the process was by no means limited

DESCRIPTION OF PLATE IV.

Illustrating Dr. F. E. Batten's communication on "Polio-encephalitis inferior." (Page 359.)

FIG. 1.—A section of the normal medulla at the level of the sixth and seventh nuclei.

FIG. 2.—Section of the medulla at the same level, showing exudation of round-cells and hæmorrhage into the tissue of the nucleus of the seventh nerve. All the vessels in this region are extremely engorged.

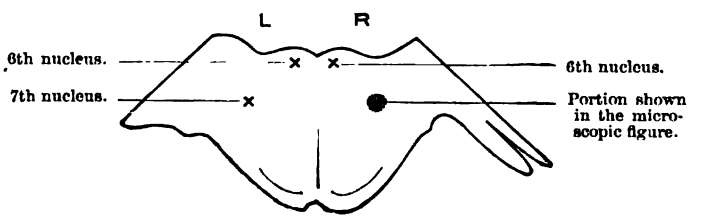


Diagram showing the relative positions of the sixth and seventh nuclei on each side; the shaded area represents the portion shown in Fig. 2.

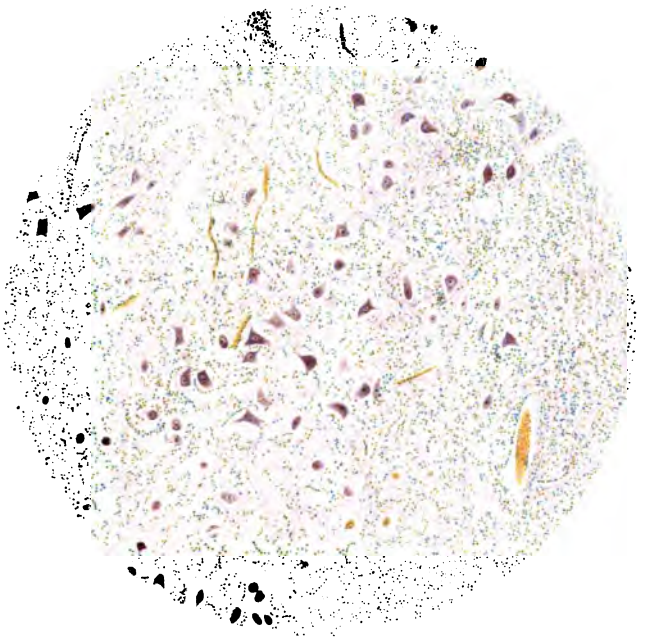


Fig.1.

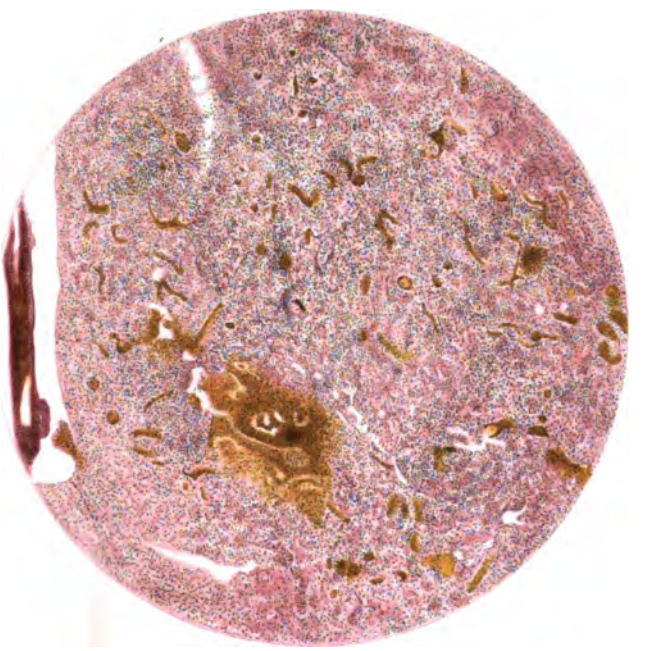


Fig.2.

Lith. Ansst. & Publ. Cole Lond.

to this region, and other areas of extreme vascular engorgement and effusion of blood into the tissue were to be found.

Stained by Nissl method, the majority of the cells of both the sixth and left seventh nuclei appeared normal. In section through the medulla at the upper end of the olive, a considerable patch of congestion is to be seen situated in the region of the ninth and tenth nuclei on the right side; and throughout the medulla, and in the grey matter of the upper portion of the spinal cord in the cervical region, there is considerable congestion and perivascular exudation. The lower cervical, dorsal, and lumbar portions of the spinal cord appear normal.

Sections through the most affected areas were kindly examined for me by Dr. Poynton for the presence of micro-organisms, but with an entirely negative result.

The most striking feature of the case is that a complete right facial paralysis should have been produced by a vascular lesion so localised that it failed to involve the nuclei in the immediate neighbourhood, *i. e.* the right sixth nucleus.

The pathological condition above described was undoubtedly due to an acute vascular lesion exactly similar to that producing an acute anterior polio-myelitis or an acute polio-encephalitis superior. The question whether such a condition is due to a primary thrombrosis of the smaller vessels, or is secondary to the invasion of the tissues by some micro-organism, is one that has yet to be decided. No organism has been proved to be present in this affection, but it may be that its habitat has yet to be discovered.

The case occurred in the month of September, 1902, during the summer of which year there were an unusual number of cases of acute anterior polio-myelitis. The summer was not a hot one; in fact, the month of August was unusually cold, and during the same period the death-rate for zymotic disease was below the average.

October 21*st*, 1902.

48. *A case of malignant endocarditis, in which the gonococcus was present in the blood and tissues.*

By Julia Cock.

The patient was an unmarried woman aged 25, and a sempstress. She was admitted to the New Hospital for Women, London, on October 28th, 1902, with a diagnosis of enteric fever. The history of her illness obtained was that on October 24th patient was quite well, and was in the City seeing the illuminations. On the morning of Saturday, the 25th, she had very severe headache, and stayed in bed. She was drowsy and slept all day on Saturday, on Saturday night, and very heavily throughout Sunday, the 26th. There was no vomiting, epistaxis, or diarrhœa. On Sunday evening she was seen by a doctor, who found the temperature 105° F. A powder was given, after which the bowels acted five times and the patient vomited. On Sunday night patient slept badly, was restless, and wandered in her talk. She did not sleep at all on Monday, the 27th, or on Monday night, and on Tuesday, the 28th, insisted on getting up. She was seen again by the doctor on Tuesday, who diagnosed enteric fever, and she was sent to the New Hospital.

Her past history was that as a child she had measles, followed by inflammation of the lungs. At twelve years old she had a second severe attack of inflammation of the lungs. She has had several attacks of influenza. The date of the last cannot be obtained. Patient had been getting thinner for the last five years, and in May, 1902, her chest was examined by a doctor, who said the left lung was affected. She has had a cough for three months. She had recently suffered from shivering attacks.

Family history.—Father living and well. Mother died, aged 36, of consumption of the bowels. Sister had acute rheumatism once. Step-sisters are subject to sore throat.

Condition on admission.—Temperature 105·6°; pulse 108; respirations 30. The patient is profoundly ill. The skin of the trunk is hot and dry; the extremities are cold. On the cheeks is a wide-spread dusky flush, with pallor round the mouth, and marked cyanosis of the lips, which are dry. A

bruise-like staining is seen at the tip of the nose, looking as if the part had been struck. The eyes are bright, and the pupils dilated and equal. The patient wanders in her talk; she expresses herself as quite well, and is anxious to get up. She fancies things are in the room, and tries to get out of bed. She does not sleep. The patient is thin, but not emaciated.

Circulatory system.—The pulse is rapid and small (108), not dicrotic, regular, tension low. Arteries not thickened. No œdema.

Heart.—No visible pulsation or thrill. No increase in the A.C.D. upwards or to the right. The maximum impulse is present in the fifth interspace just within the left nipple line. The first sound at the apex is replaced by a loud, harsh systolic murmur, conducted to the posterior axillary line.

In the pulmonary area the first sound is soft and the second sound accentuated.

In the aortic area both sounds are distinct, and there are no murmurs.

The heart's action is regular, and its pulsations are all represented at the wrist.

Respiratory system.—The chest-wall is thin and the thorax well formed. The note is everywhere resonant to percussion, and breath-sounds are vesicular. A few rhonchi are scattered over the chest. No cough or expectoration.

The tongue is dry, red at the tip and edges, covered with a thick fur, and slightly tremulous. The bowels are confined.

The abdomen is slightly distended, and is somewhat difficult to examine. No pain or tenderness is present, no organs are felt, and the appendix and gall-bladder regions present nothing abnormal. No spots are present.

The urine has a sp. gr. of 1020, is dark in colour, scanty, contains a thick cloud of albumen, no casts, and no sugar; urea 2·4 per cent.

Progress briefly as follows:

October 30th.—Temperature varies between 103° and 104°, and is hardly influenced by the external application of cold. Patient is excitable and restless, and does not reply to questions. There is marked tremor of the hands, lips, and tongue. Sleep is not obtained. No rigors or sweating. No diarrhœa. The abdomen is less distended, but nothing abnormal can be detected

on examination. Examination of the heart shows no involvement of fresh valves. The murmur at the apex is as before. Nothing abnormal is detected in the lungs, but a few frictions are heard along the left border of the sternum.

31st.—Patient has lost flesh, and the face is now livid and dusky. She mutters to herself and complains of headache. Tremor is very marked. Erythematous patches are present on the right elbow and forearm, and bluish petechiæ have appeared on both forearms, and on the first finger of both hands, near the nail and on the palmar aspect. Bruise-like discoloration of the skin is present on the left knee and on the dorsum of the left foot. Patient vomited twice. A formed stool was passed. The blood was tested for Widal's reaction with a negative result. Urine 1025; acid; much albumen present; no blood; no diazo reaction; numerous casts are present, chiefly hyaline. Temperature 103°—104°.

November 1st.—Widal's reaction absent. A culture of the blood shows staphylococci. Patient is semi-stuporous, is passing evacuations under her, and there is difficulty in getting food taken. Percussion note impaired at the left apex in front to upper border of third rib. Breathing laboured; alæ nasi working. Respirations 40 per minute. Pulse rapid, running, and uncountable at the wrist. Temperature 104·8°. Systolic bruit at apex distinct. No further alteration in the condition of the heart. Patient is rigid; there is semi-convulsive tremor of the limbs on passive movement. The elbows, wrists, and knees are flexed, the ankles extended. Patient is quite unconscious, and mutters to herself.

2nd.—Patient cannot swallow, and is fed by nasal tube. Rigidity and tremor continue. Head retracted. Impairment of note at both bases, and air-entry diminished. Widal's reaction not present.

3rd.—Condition unchanged. Fresh petechial patches have appeared on right forearm. Temperature 103·6°. Ophthalmoscopic examination shows the fundus to be normal.

4th.—Patient remained in the same condition until 6 p.m., when the rigidity and tremors became less marked. No further change detected in heart or lungs. The tongue is dry and black; the lips are dry and show black petechial patches.

5th.—At 7 a.m. Cheyne-Stokes breathing was present. The

left pupil was smaller than the right; both reacted to light. The pulse failed slowly, and patient died at 4 p.m. Temperature at time of death, 101·6°—this being the first reading below 102° since the patient came under observation.

The treatment consisted in (*a*) attempts to reduce the temperature by the external application of cold; (*b*) stimulation by alcohol, strychnine, and digitalin. The use of antistreptococcic serum was discussed, and negatived, as the blood culture did not show the presence of streptococci.

The diagnosis made during life was of some virulent septic condition with malignant endocarditis. No source of sepsis was discovered, though it was carefully searched for. From the history obtained from the friends as to the patient's manner of life it was thought possible that the infection might prove to be gonorrhœal in origin.

Shortly after death an attempt was made through the chest-wall to obtain blood from the ventricle with a sterilised syringe. Pericardial fluid was obtained which on examination proved to be sterile.

The autopsy was made seventeen hours after death. Rigor mortis was present. *Post-mortem* staining is considerable, and the petechial spots present during life persist.

Pleuræ.—On opening the thorax a few delicate recent adhesions are seen at the apex of the right pleural cavity anteriorly. On the left side anteriorly there are tougher adhesions in the pleural cavity extending from the apex to the third rib. These are old. No effusion is present; no hæmorrhages are seen on the pleura, which appears healthy.

Lungs.—The left lung is congested, the lower lobe intensely so, and this lobe contains at its inferior border one large recent infarct. No patch of pneumonia. The right lung is congested; the base is nearly solid. No patch of pneumonia or area of infarction present.

Pericardium.—In the pericardial cavity is about ʒij of blood-stained fluid and a small blood-clot, the clot and blood-staining being due probably to the puncture made in an attempt to obtain blood from the heart shortly after death. The serous surfaces are smooth and bright, and there is not the least trace of pericarditis. No hæmorrhages are present.

Heart.—The heart is not enlarged. Over its surface, as seen

through the visceral layer of pericardium, are plentifully scattered irregular patches of hæmorrhage, varying in size from a pin's head to a small bean. They are most marked near the apex and on the anterior aspect, where they are thickly clustered. They vary in colour between dull crimson and purple. In addition are also seen numerous cream-coloured patches of irregular shape, and surrounded by a narrow purplish areola. These have the appearance of suppurating foci; some are definitely raised above the surface, but the larger number are flush with it. The vessels are unusually prominent, and deeply injected.

The right auricle and ventricle contain much chicken-fat clot. There is no injection of the endocardium, no roughened patches, no granulations, and the valves are healthy.

The left ventricle is empty. The mitral valve is thickened, puckered, and shows evidence of old endocarditis. At the edge of the anterior cusp are lumpy, fungating masses of recent vegetations, much raised above the surface of the valve, and detached from it with great ease. At the base of the valve on the ventricular aspect are three large recent vegetations, injected and roughened. The largest is the size of a small bean, and all have a friable texture and a distinctly worm-eaten appearance, as of recent disintegration and destruction. Portions of these granulations are readily detached. In addition is an irregular area on the auricular surface near the base of the valve, measuring ½ inch by ¼ inch, which is roughened and disintegrated, and over which the endocardium is destroyed. The endocardium of the ventricle is injected, and the heart-wall shows a considerable number of small yellowish patches similar to those seen on the external surface. Similar yellowish points surrounded by an areola of injection are present in the substance of some of the columnæ carneæ, and some of these are adherent to each other by fine inflammatory bands. In the substance of the heart-wall similar appearances are present, viz. softened yellowish patches of irregular outline, which appear to contain pus. The weight is 10 oz.

Kidneys weigh together 10½ oz. They are soft, deeply injected, and bleed readily on section. The capsule strips, and is not thickened. Very numerous hæmorrhages are seen scattered over the surface and in the substance of the cortex. They vary in size from a hemp-seed to a bean, and are irregular in outline.

In addition numerous yellowish patches are present, some as large as an almond, some much smaller. These are surrounded by a narrow scarlet areola, fading off into purple. These patches have the appearance of embolic abscesses.

The bladder and ureters appear normal.

The spleen weighs 7½ oz. It is enlarged, semi-diffluent, deeply congested, and contains numerous infarcts, some recent, some older and necrotic.

The liver is normal in appearance; weight, 52 oz.

The gall-bladder and ducts are healthy, and contain no stone. No evidence of inflammatory processes is present.

The peritoneum is healthy. No fluid is present.

The retro-peritoneal glands are enlarged from pelvis to thorax, and somewhat softened. No hæmorrhages are present.

The stomach shows an oval patch of purplish discoloration on the anterior wall, towards the cardiac end of the lesser curvature. Near the centre of this patch is a greyish-yellow nodule the size of a small hemp-seed, raised above the surface. Similar nodular swellings are present throughout the whole intestinal tract as far as the anus, some situated on discoloured patches as in the stomach, some on apparently normal mucous membrane. They vary in size from a pin's head to a pea. Numerous similar nodules are present in the mesentery. None are ulcerated.

The appendix is healthy. It is long, runs down into the pelvis, and is adherent to the right ovary. It contains one of the nodules mentioned as occurring in the intestine.

The ovaries and tubes are much matted. Both sides are affected equally. The tubes are patent, their walls are thickened, and the cavities contain a small quantity of yellowish exudation. The fimbriated ends are thickened and adherent to ovaries and surrounding parts.

The uterus is not enlarged. The endometrium is thickened and œdematous-looking. Small purplish patches are seen scattered over its surface, and the cavity contains a small quantity of muco-purulent material.

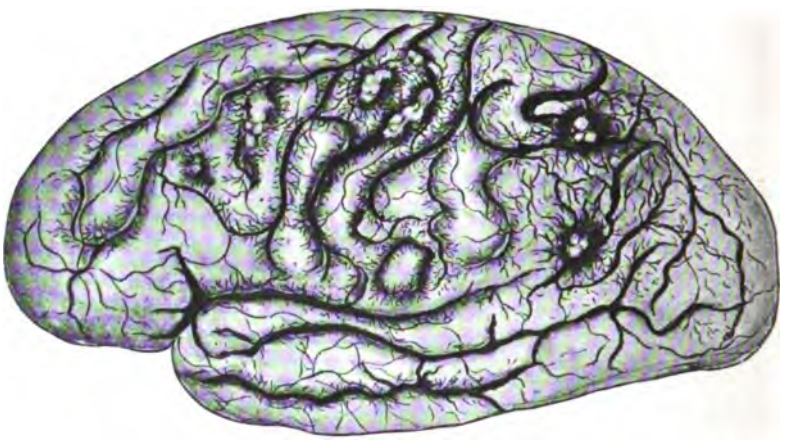
The vagina and external parts show nothing noteworthy.

Brain.—The dura-mater is normal. No clotting in the longitudinal sinuses. The pia-mater is much injected. No pus. Fluid is clear and not in excess. The cortical surface of the brain is deeply injected, and scattered over it are a number of super-

ficial yellowish areas of irregular shape, surrounded by a border of deep congestion. They vary in size from a large pin's head to a lentil, and tend to arrange themselves in small groups of two or three. They are not raised above the surface. These patches are present only over the external and upper surface. The greater number are over the frontal lobe, a few over the parietal and occipital lobes. None are present over the temporo-sphenoidal lobe. The base is healthy, and after hardening nothing abnormal was detected in the substance of the brain.

The ears are healthy.

FIG. 34.



The outer surface of the left hemisphere, showing the small suppurating foci described in the text.

Bacteriology.

The pericardial fluid withdrawn shortly after death was examined bacteriologically, and was sterile. No growth appeared in any of the media inoculated from the fluid, and incubated aërobically and anaërobically. Cover-smear preparations made from centrifugalised deposit showed extremely few cells, and no micrococci or other organisms have been identified. The fluid was serous.

The blood withdrawn from the left ventricle seventeen hours after death in a sterilised syringe, gave the following results:

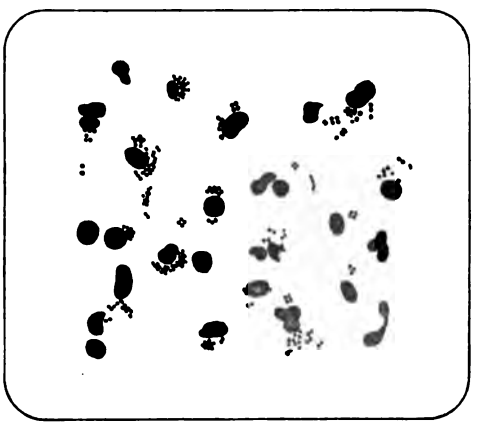
In cover-smear preparations made direct from this blood a fair

number of micrococci are present. In a smear stained by Gram's method it is found that the micrococci are of two kinds, one staining and the other not retaining the Gram's stain. The latter appear as diplococci, in which occasionally a reniform shape can be traced. Cultivations show *Staphylococcus pyogenes aureus* in pure culture.

Both organisms have been identified also in the abscesses in the brain and kidney.

The kidney shows extremely numerous septic foci, many

FIG. 35.



The contents of one of the small cerebral abscesses, showing leucocytes, and two forms of cocci—tetrads and diplococci (gonococcus),—with clusters of *Staphylococcus aureus*. Preparation stained with methylene blue. × 840.

necrotic, but some in earlier stages of inflammatory exudation. The general condition is one of the most intense septic nephritis.

The nodules in the intestine, to which reference has been made, consist in inflammatory swelling of the normal lymphoid structures of the part. None of those examined had become necrotic.

The *septic foci* in the brain are very superficial, confined to the cortex, and are unaccompanied by any deep-seated lesions. No degeneration of nerve tissue was found in the sections stained and examined for this purpose.

This case seems worthy of record as being one of the earliest in this country in which an organism having the morphological

A microscopic section of the kidney showing two necrotic and suppurating foci.

purely gonococcal, but was mixed—the gonococcus being present in association with *Staphylococcus pyogenes aureus.*

Clinical points of interest are—

(*a*) The intense virulence and short course of the illness,

death occurring in ten days from the onset, and the patient showing profound nervous prostration within thirty-six hours of onset, which was very sudden.

(*b*) The absence of rigors and of involvement of joints.

I owe much in the investigation of this case to the kind help of Miss Chadwick, Miss Debenham, Dr. Mabel Jones, and Mr. G. L. Eastes.

REFERENCES.

1. *Bourdon.*—'Gaz. d. Hôp.,' 1868, xii, p. 1.
2. *Desnos.*—'L'Union méd.,' 1878, xxv, p. 43.
3. *Schedler.*—'Inaug. Diss. Berlin,' 1880.
4. *Draper.*—'Medical Bulletin, Philadelphia,' 1882, iv, p. 81.
5. *Martin.*—'Rev. méd. de la Suisse Romande,' 1882, ii, pp. 308, 352.
6. *Fleury.*—'Journ. de méd. de Bordeaux,' 1883–4, xiii, p. 65.
7. *Weckerle.*—'Münch. med. Woch.,' 1886, xxxiii.
8. *Weichselbaum.*—'Centralbl. f. Bakt.,' 1887, ii, p. 209; *also* Ziegler's 'Beiträge,' 1889, iv, p. 125.
9. *Rothmund.*—'Dissertation Zürich,' 1889.
10. *Ely.*—'Med. Record,' 1889, xxxv, p. 287.
11. *His.*—'Berl. klin. Woch.,' 1892, xxix, p. 993.
12. *His.*—Op. cit.
13. *Leyden.*—'Deutsch. med. Woch.,' 1893, xix, p. 909.
14. *Wilms.*—'Münch. med. Woch.,' 1893, xl, p. 745.
15. *Golz.*—'Inaug. Diss. Berlin,' 1893.
16. *Councilman.*—'Amer. Journ. Med. Sci.,' 1893, cvi, p. 540.
17. *Fressel.*—'Inaug. Diss. Leipsic,' 1894.
18. *Winterberg.*—'Festschrift z. 25 Jahr. Jub. des Vereins Deutschr. Aerzte zu San Francisco,' 1894, p. 40.
19. *Thayer and Blumer.*—'Johns Hopkins Hosp. Bull.,' 1896, vii, p. 57.
20. *Finger, Ghon, and Schlagenhaufer.*—'Arch. f. Dermat. u. Syph.,' 1895, xxxiii, p. 141.
21. *Zawadski and Bregman.*—'Wien. med. Woch.,' 1896, xlvi, p. 313.
22. *Dauber and Borst.*—'Deutsch. Arch. f. kl. Med.,' 1896, lvi, p. 231.
23. *Michaelis.*—'Zeitschr. f. kl. Med.,' 1896, xxix, p. 556.
24. *Keller.*—'Deutsch. Arch. f. kl. Med.,' 1896, lvii, p. 387.
25. *Hale White.*—'Lancet,' 1896, i, p. 533.
26. *Babes and Sion.*—'Arch. d. Sc. méd. de Bucharest,' 1896, i, p. 505.
27. *Stengel.*—'Univ. Med. Mag. Philadelphia,' 1897, ix, p. 426.
28. *Thayer and Lazear.*—'Journal of Experimental Medicine,' Jan., 1899, p. 81; *also* XII International Congress, Moscow, 1897.
29. *Rendu and Hallé.*—'Bull. et mém. Soc. méd. des Hôp. de Paris,' 1897, xiv, p. 1325.
30. *Siegheim.*—'Zeitschr. f. kl. Med.,' 1898, xxxiv, p. 526.
31. *Lenharz.*—'Berl. kl. Woch.,' 1897, xxxiv, p. 1138.

32. *Harris and Johnston.*—'Bull. Johns Hopkins Hosp.,' 1902, xiii, p. 236.
33. *Lartigan.*—'Amer. Journ. Med. Sciences,' Philadelphia, 1901, cxxi, pp. 52—59.

Note.—The above references are chiefly obtained from the paper by Drs. Thayer and Lazear (28).

May 19th, 1903.

Addendum to Dr. F. P. Weber's communication on acute leukæmia (page 286).

SINCE writing this paper an article on "Acute Myelogenic Leukæmia," by Dr. Billings and Dr. Capps, has appeared in the 'American Journal of Medical Sciences' for September, 1903 (p.375). They regard the faintly granular, large mononuclear cells in the blood of Obrastzow's and similar cases as myelocytes or transitional cells. Their views are not much at variance with those here expressed.

The bone-marrow must be the source of the great increase of the so-called "lymphocytes" in the blood of those cases of acute leukæmia in which the bone-marrow is practically the only one of the leucocyte-forming tissues involved—no matter whether these cells be termed "lymphocytes," or "non-granular myelocytes," or "myelocytoblasts" which have not yet had time to form granules in their cell-protoplasm. I incline to the view that cells of the large non-granular mononuclear type, whether in the bone-marrow, or in the lymphatic glandular tissue, or in both of them, can give rise not only to cells of the ordinary lymphocyte type, but also to cells of the myelocyte type. All varieties of leukæmia can be accounted for in this way. In Dr. Wilkinson's case ('Lancet,' 1903, vol. i, p. 1739) the blood condition is said to have changed from one of myelogenic leukæmia to one of lymphatic leukæmia. The lymphatic glands were not felt enlarged. No *post-mortem* examination was obtained, but I think that the change in the type of the blood-cells may very well be explained by supposing the bone-marrow disease to have become more acute. Thus the leukæmic condition of the blood would become "less differentiated," *i. e.* the large non-granular mononuclear cells (lymphocyte-like cells) would remain undiffer-

entiated, not having time to develop into granular cells of the myelocyte type. Doubtless also in acute exacerbations of chronic myelogenic leukæmia, as well as in primarily acute myelogenic leukæmia, the blood may show an enormous increase of cells of the large mononuclear (lymphocyte-like) type.

An important physiological deduction from a study of cases of "multiple myeloma of the lymphatic type" (*i. e.* lymphadenomatosis ossium) and cases of acute lymphocythæmia, in which the bone-marrow is the only one of the blood-forming tissues involved, is that all the granular myelocytes (and consequently all the polymorphonuclear leucocytes of the blood-serum) are to be regarded as normally derived from cells of the lymphocyte type, *i. e.* as being *differentiated lymphocytes.* When an extremely rapid formation of myelocytes is attempted (hyperplasia-like tumour-formation in the bone-marrow) there is no time for the development of granules in the cell-protoplasm, and consequently cells resembling large and small lymphocytes, not myelocytes, are produced.

In my classes A and B of the group of leukæmias and pseudo-leukæmias, instead of supposing that the lymphocyte-like cells are derived from the non-granular predecessors of the myelocytes, I would now suggest that they are derived from the myelocytes themselves by the latter losing their granulation in the process of proliferation, and consequently reverting to the lymphocyte-like (embryonal) type of their ancestors. According to this theory the large lymphocyte-like cells would represent ordinary large myelocytes, and the small lymphocyte-like cells (generally fewer in number) would represent particularly small myelocytes.

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